American Heart Journal

An international publication for the study of the circulation

George E Burch *Editor*

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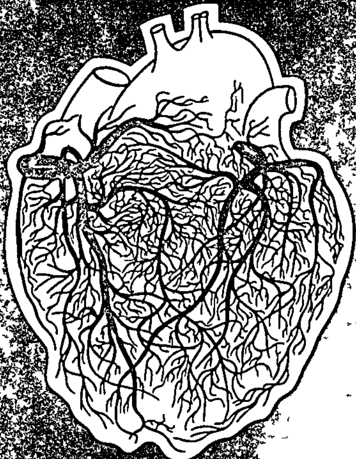
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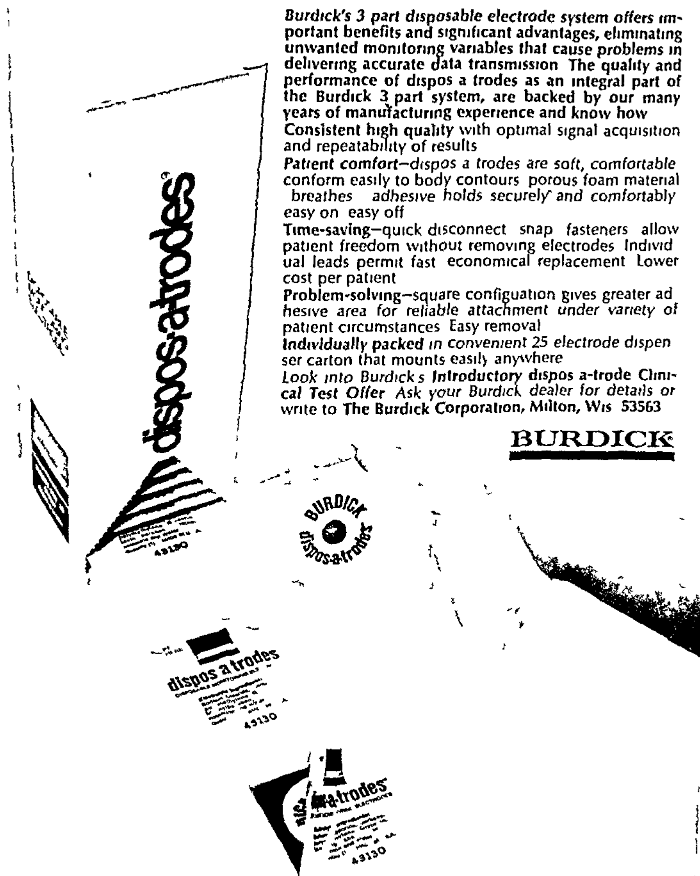
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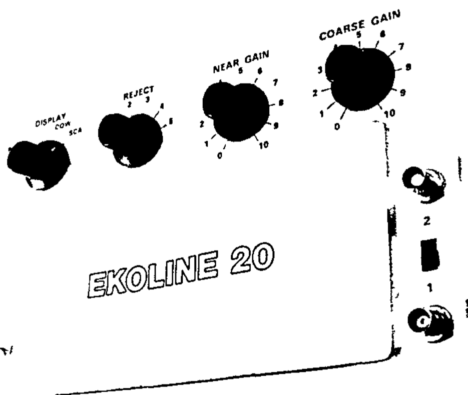
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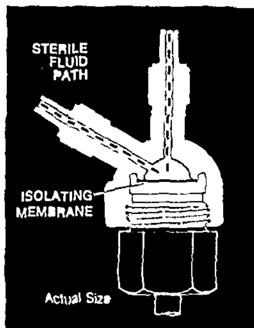
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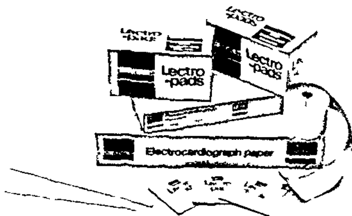
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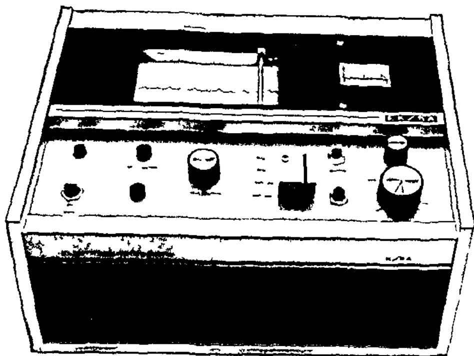
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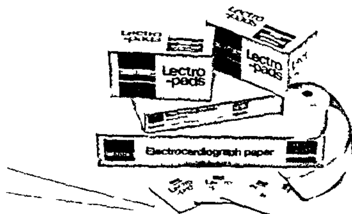
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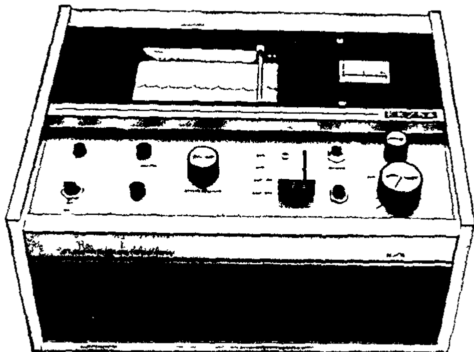
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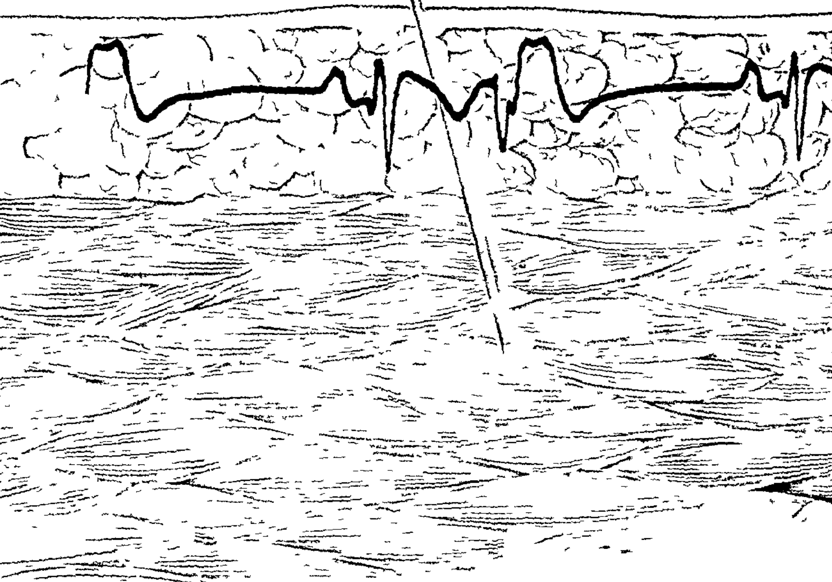
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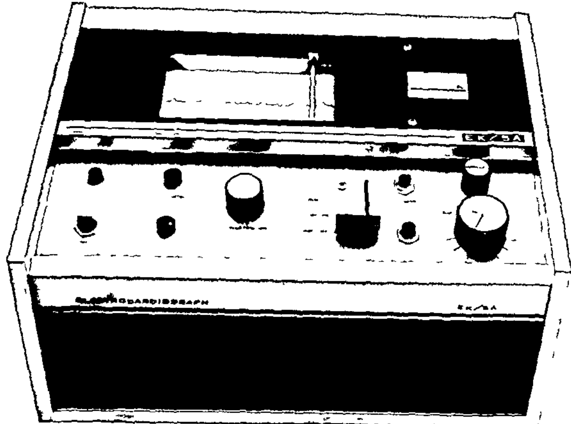
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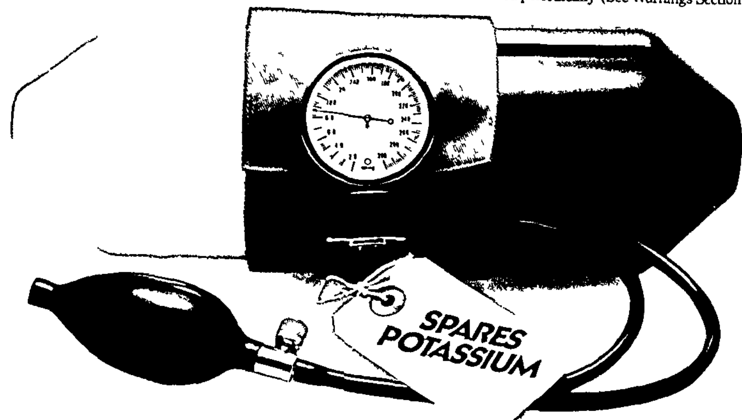
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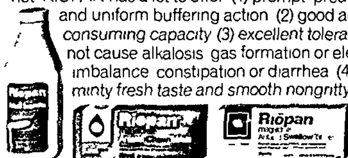
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American Heart Journal

July 1975 Volume 90 Number 1

Editorial

New aspects of the thrombogenic effect of oral contraceptives

B Astedt MD
Malmö Sweden

Investigations of the association between hormonal contraceptives and thrombosis are confusing to many clinicians This is hardly surprising since extensive epidemiologic studies as well as investigations of changes in the blood and in vessel walls have given conflicting results or the findings have been interpreted differently by different authorities

The epidemiologic studies [illegible] have recently been critically reviewed in this journal by Hougie[7] and the literature on coronary thrombosis and oral contraceptives has been surveyed by Maleki and Lange[8] Judging from these papers the relationship between the use of oral contraceptives and thrombotic disease is still debatable

According to some authors the estrogenic component of oral contraceptives has been held responsible for the possibly thrombogenic effect of the pill[9-11] an effect denied by others [illegible] The use of estrogens in the treatment of certain conditions has also been reported to have a thrombogenic effect The frequency of thrombosis is still higher in women given diethylstilbestrol[12] and ethinylestradiol[1] to suppress lactation Oliver found the frequency of thrombotic conditions to increase in men treated with ethinylestradiol to depress the blood cholesterol level Bailar[15] found the use of diethylstilbestrol in the treatment of prostatic carcinoma to increase the mortality from cardiovascular complications Gow and MacGillivray[16] reported a high incidence (16 per cent) of venous thrombotic disease in oophorectomized women treated with ethinylestradiol

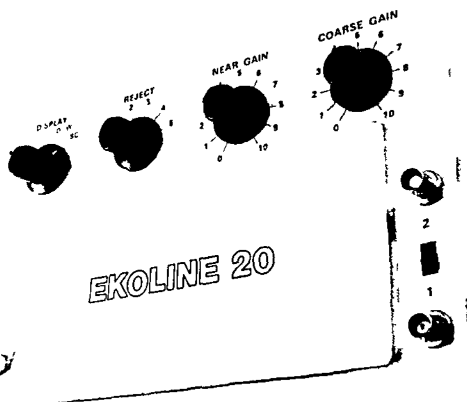
Because of the suspect thrombogenic effect of estrogens the Committee on Safety of Drugs recommended that estrogen content of oral contraceptives mestranol or ethinylestradiol should not exceed 50 μg But recent evaluation of this recommendation by Vessey and Inman[17] revealed no significant reduction in the frequency of thromboembolism among users of oral contraceptives

Interesting contributions have however recently been made to the body of knowledge in this realm Thus Badaracco and Vessey[18] followed up 42 women who had had a thrombotic episode earlier during the use of oral contraceptives and 42 women who had had such an attack but not used oral contraceptives The risk of recurrences during pregnancy and in the puerperium were equally common in both groups while recurrences not associated with pregnancy were four times as common among women who had not used oral contraceptives in association with the earlier thrombotic episode This suggests a differ

From the Coagulation Laboratory and Department of Gynecology and Obstetrics, Allmänna Sjukhuset University of Lund Malmö Sweden.

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Reprint requests Birger Åstedt MD Department of Gynecology University of Lund, Allmänna Sjukhuset 214 01 Malmö Sweden



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selected cases where the use of oral contraceptives is of importance In other doubtful cases contraceptives containing only progestogens might be used until natural estrogens have proved a suitable component of oral contraceptives

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ence in the inherited disposition to thrombosis between the groups Thrombosis during the use of oral contraceptives might, therefore, be due to some defect easily influenced by hormones

Such an inherited defect has actually been shown Åstedt and co workers[19] examined the coagulation factors and components of the fibrinolytic system in 31 women who had previously had phlebographically verified thrombosis during the use of oral contraceptives The investigation was undertaken six to twelve months after the thrombotic episode by which time the metabolic effect had worn off Abnormalities, particularly in the fibrinolytic defense system were found in most of the patients The most common defect was a low content of fibrinolytic activators in the venous vessel wall One might, therefore wonder whether the patients would sooner or later have had thrombosis even if they had not used oral contraceptives

But it has also been shown that particularly the fibrinolytic activators, which are of importance in the prevention of thrombosis, respond to hormones When ethinylestradiol was given in a large dose of 250 μg a day for 10 days to women who were to be operated upon because of uterine prolapse the fibrinolytic activator content of the vessel wall fell significantly[20] This dose is five times as large as that used in oral contraceptives However in some patients with a defective content of fibrinolytic activators in the vessel wall the fibrinolytic activity might be very close to the critical level, i e, that below which thrombosis is apt to occur The estrogenic effect in such sensitive patients might perhaps lower the activator content below the critical level

Estrogens seem to be a necessary component of most oral contraceptives as pure prostagenic preparations because irregular bleedings are not acceptable to many women Interest has, therefore, been focused on the natural estrogens The use of natural estrogens as a component in oral contraceptives has hitherto failed because they were not readily absorbed but this pharmacologic problem has now been solved There is now some evidence that 17 beta estradiol does not suppress the fibrinolytic defense system to the same extent as ethinylestradiol (Astedt and Jeppsson 1974 to be published)

As for the relation between oral contraceptives and myocardial infarction, a recent epidemiologic investigation suggested such an association in women in whom the risk of such infarctions was increased for other reasons[21] But to elucidate a possible association, investigations similar to those mentioned above should be undertaken It is of interest to note that the fibrinolytic activity of vessels is localized mainly to the vasa vasorum[22] Ontogenetically, the coronary vessels of the heart might be regarded as the vasa vasorum of the organ which are actually the site of most of the fibrinolytic activity[23, 24] The considerations of a critical suppression of the fibrinolytic activator content of the vessel wall by estrogens thus to a great extent, could be applied to the heart vessels

In the last few years interest also has been focused on the significance of antithrombin III It has been found to be reduced by about 15 per cent in women using combined oral contraceptives[25] Howie and co workers[6] found the synthetic estrogenic compound, mestranol to lower the antithrombin III activity and thereby indicate that the estrogenic component of oral contraceptives is responsible for this reduction But the significance of antithrombin III in the development of thrombosis is also debatable Only a few families with low antithrombin III activity and occurrence of thrombotic episodes are known[27, 8] Von Kaulla and von Kaulla[28] reported the concentration of antithrombin III to be low in the acute stage of thrombotic conditions But, in patients with recurrent thrombosis and examined during a remission the concentration of antithrombin III has been found to be normal[9] A low concentration of antithrombin III, therefore, seems not to be a characteristic of patients predisposed to thrombosis In the investigation of women during remission who had previously had thrombosis during the use of oral contraceptives the concentration of antithrombin III was normal[19] indicating that this test is of no value for detecting patients predisposed to thrombosis

Neither has the search for another simple test to identify women predisposed to thrombosis hitherto been successful Careful inquiry into the woman s history for earlier thrombotic episodes or ischemic heart disease is still necessary for deciding whether oral contraceptives containing estrogens should be avoided Examination of the most important and common defect of the fibrinolytic defense system i e the content of fibrinolytic activators in the vessel wall makes a venous biopsy necessary This can be performed in

selected cases where the use of oral contraceptives is of importance In other doubtful cases contraceptives containing only progestogens might be used until natural estrogens have proved a suitable component of oral contraceptives

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Velocity of contractile element shortening in constrictive pericarditis and the effect of pulsus paradoxus

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M S Gotsman M D, F R C P, F A C C
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In constrictive pericarditis (CP) the left ventricle (LV) is compressed by a thick rind of caseous, fibrous, or calcified material Patients with CP have an unusual aberration of ventricular function the ventricle is compressed and small but the ejection fraction and fractional shortening of the fibers remains constant A small stroke volume is ejected in patients with severe compression and a decrease in end diastolic volume The unusually high LV end diastolic pressure and the apparent decrease in compliance is probably a consequence of the fibrous extrinsic compression [1] We have asked the question is there an abnormality of muscle fiber function in constrictive pericarditis?

This study will analyze in detail the force velocity curves and the calculated isovolumic indices of ventricular celerity in nine patients with CP to determine whether these are altered to assess their value under abnormal loading conditions and to study the effect of beat to beat variation in preload (pulsus paradoxus) In a second part of this study the patients with CP will be compared with another group of patients with elevated diastolic pressures as a result of congestive cardiomyopathy (CMO) and with another two control subjects

Patients

A group of nine consecutive patients with CP who were investigated before the operation of pericardiectomy were selected for this study The patients were all in cardiac failure and received digitalis therapy their clinical disability is shown in Table I Histology showed that the constriction was of tuberculous origin in eight patients and bilharzial in one patient

Another four patients with CMO were also studied one patient was studied to exclude coronary artery disease and informed consent in the appropriate language was obtained from all the patients prior to investigation Two patients with Grade 4 disability had trivial mitral incompetence demonstrated on angiography with regurgitant fractions calculated to be 20 and 25 per cent respectively [2] All the patients received digitalis

Two patients with chest pain resembling angina pectoris had normal hemodynamics and angiographic findings at cardiac catheterization Their data were compared with those of the patients in the first two groups

Methods

Data acquisition Patients were studied in the fasting state Premedication with 10 mg of diazepam and 50 mg of pethidine was given one hour before study Routine right and left heart catheterization was performed via percutaneous puncture of the femoral vein and artery Left heart pressure measurements were made using a Statham SF1 micromanometer tipped catheter, right heart pressures were measured with a fluid filled catheter manometer system and Statham P23 Db bonded strain gauge the system was carefully debubbled and the frequency response was flat to 20 Hz Pressure recordings were made at a paper speed of 200 mm per second on an Electronics for Medicine DR 16 photographic recorder with an electronic analog differentiating

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circuit which has minimal phase lag and distortion The LV pressure recording and its simultaneous first derivative were carefully digitized manually at 5 msec intervals and analyzed using a Wang 700C programmable calculator with plotter printer output

Cardiac output was measured by the indicator dilution method using 5 mg of indocyanine green a Gilford optical densitometer and a Harvard constant infusion and withdrawal pump sampling at a constant rate of 38 ml per minute The procedure was completed by left ventriculography in the right anterior oblique (RAO) position using a slow injection of 50 ml of 76 per cent Urografin with continuous measurement of ascending aortic pressure using a second catheter introduced in the contralateral groin In patients with angina pectoris selective coronary angiography showed normal major coronary arteries

Control measurements of LV pressure and its first derivative were made with the patients in the supine position The patients legs were then passively elevated to a height of 24 inches and the measurements repeated after three to five minutes The patient was allowed to rest supine and recover and was then given an intravenous bolus of 6 μg of isoprenaline sulfate Pressure recordings were made at the time of peak tachycardia

Data calculation We measured and calculated the following *indices of ventricular* celerity during isovolumic LV systole

$$\text{Peak LV}dp/dt \qquad (1)$$

$$\text{Max } dp/dt/IP \qquad (2)$$

where IP = intraventricular pressure at time of peak LVdp/dt

$$V_m \text{ and peak } V \quad (V_m)$$

(2-element model Hill) (Voigt model) (3)

Force velocity curves were constructed according to the method of Mason and colleagues[6] The velocity of the contractile element (V) was calculated from the formula

$$V = \frac{dp/dt}{32P}$$

where P = absolute LV pressure

The point of inflexion of the curve was measured (V_m or peak V)[1] and the descending limb of the curve was extrapolated to zero load by linear extrapolation to define V_m

V_m V V (Maxwell 3 element model) (4)

The force velocity curves were plotted again using the Maxwell (3 element) model

$$V_{ce} = \frac{dp/dt}{32P}$$

where P = developed intraventricular pressure

The end diastolic pressure was measured at the instant of onset of LV pressure rise (determined visually) and corresponded to a dp/dt of 80 to 120 mm Hg per second The force velocity curve was extrapolated to zero load from 5 mm Hg developed pressure to define V_m Contractile element velocity was also measured at a developed pressure of 5 and 10 mm Hg (V , V_{10})

The force velocity curves were constructed from duplicate beats in the control subjects and in patients with CMO duplicate curves were almost identical In patients with CP beat by beat analysis was made over a respiratory cycle in four patients to study the effect of pulsus paradoxus the mean values over several respiratory cycles were calculated in all patients with CP and these values were used for comparison with patients with CMO and the control subjects

Ventricular volumes were calculated from the uniplane cineangiogram[9] and *ejection fraction* (EF) was calculated where

$$EF = \frac{\text{end diastolic volume (EDV)} - \text{end systolic volume (ESV)}}{\text{EDV}} \times 100\%$$

The mean velocity of circumferential *fiber shortening* (mean V_{cf}) was calculated from the cineangiogram

$$\text{Mean } V_{cf} = \frac{EDD - ESD}{LVET \times EDD} \times 10^3 \text{ circ/sec}$$

where EDD = transverse end diastolic diameter of the LV ESD = transverse end systolic diameter of the LV and LVET = left ventricular ejection time (milliseconds) measured from the ascending aortic pressure pulse tracing recorded during left ventriculography

Critique of methods Extrapolation of the force velocity curve to zero load defines V_m The curve is theoretically hyperbolic but in patients with high LV end diastolic pressures there are few points on the descending limb of the curve (2 element model) and we have used linear extrapolation for our calculations When the 3 element model is used LVEDP is critical in the calculation of developed pressure We have determined LVEDP visually and this corresponds to a dp/dt

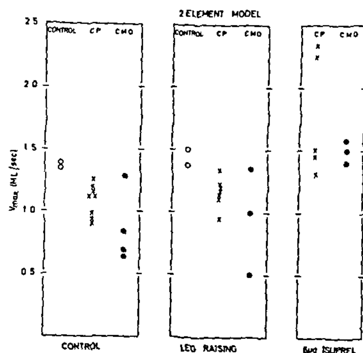


Fig 1 V_m measurements (calculated from a 2-element model) in control subjects patients with constrictive pericarditis (CP) and congestive cardiomyopathy (CMO) V_m is low in CMO except in one patient with mild disease (t = 2 26 ns) it is reduced in CP (t = 2 81 p<0 05) It does not change significantly after raising the legs but increases after a challenge of intravenous isoprenaline sulfate Isoprenaline sulfate was not given to the normal subjects and patients in whom the pressure recordings were not technically perfect have been excluded

of 80 to 120 mm Hg per second The curves may be different if a different arbitrary dp/dt is used to define LVEDP (e g , 200 mm Hg per second) this makes data in the literature difficult to compare

Respiratory gymnastics and the subsequent delivery of a large volume of contrast medium during angiography disturbs the steady state of the circulation[10 11] Angiographic volumes are used as a standard of reference for measurement of ventricular volume but we are hesitant to accept this without reservation We used only technically perfect angiograms free of ectopic beats in our calculations Measurements of left ventricular volume and particularly end systolic volume are less reliable when the ventricle is small, in these circumstances the ventricle is irregular and muscle trabeculae and papillary muscles encroach on the cavity, moreover, the use of uniplane cineangiography facilitates greater magnification of errors in measurement

Statistical analysis The results were analyzed using a Wang 700C programmable calculator and standard statistical methods

Table I The patients

	Age	Sex	Race	Etiology	Disability grading*
Group 1 Constrictive pericarditis					
1 D M	49	M	B	Tuberculosis	2b
2 D M	21	F	B	Tuberculosis	3
3 M G	35	F	B	Tuberculosis	3
4 A M	52	M	B	Tuberculosis	3
5 K Z	16	F	B	Bilharziasis	3
6 M K	33	M	B	Tuberculosis	3
7 T M	52	M	B	Tuberculosis	3
8 S M	27	M	B	Tuberculosis	4
9 V N	23	F	B	Tuberculosis	4
Group 2 Congestive cardiomyopathy					
10 M M	57	M	B	Unknown	1
11 S C	25	M	As	Unknown	2b
12 A S	37	M	B	Unknown	4
13 J M	68	M	B	Unknown	4
Group 3 Control subjects					
14 A R	36	M	As		
15 L C	22	M	As		

New York Heart Association Grading at time of study
B = Bantu As = Asiatic

Results

The measured and derived hemodynamic and angiographic data are given in Tables II and III

Peak LVdp/dt Peak LVdp/dt was normal or slightly reduced in patients with CP (1 113 ± 259 mm Hg per second) It was greatly reduced in patients with CMO except in one patient who had mild disease (948 ± 334 mm Hg per second)

Max dp/dt/IP Max dp/dt/IP was normal or reduced in CP (15 2 ± 2 8 sec^{-1}) compared with a mean value of 12 9 ± 2 9 sec^{-1} in CMO and 18 4 sec^{-1} in the control subjects

V_{max} (2 element model) (Hill or Voigt model) When patients with CMO were compared to the normal subjects, V_{max} was depressed in CMO (except in one patient with mild disease) (mean V_m = 0 86 ± 0 30 ML per second) (t = 2 26, ns) V_{max} was also reduced in patients with CP (1 09 ± 0 13 ML per second) (t = 2 81 $p < 0 05$) (control value = 1 37 ML per second) (Fig 1 Table III)

V_m correlated closely with peak LVdp/dt Max dp/dt/IP, and mean V_{cf} (Fig 2) Fig 3 shows the relationship between the velocity measurement, V_m and the length measurement EF, and separates the three groups of patients the control subjects have a normal V_m and normal EF while three patients with CMO show great reduction in

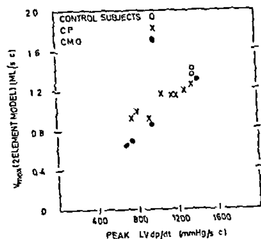


Fig 2 Linear relationship between peak LVdp/dt and V_m (V_m =0 150 + 0 001 Peak LVdp/dt±0 096 r=0 91 t=7 60 p<0 001) An identical relationship exists between Max dp/dt/IP and V_{max} (V_{max}=0 013+0 070 Max dp/dt/IP±0 108 r=0 89 t=6 76 p<0 001)

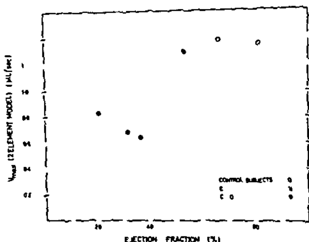


Fig 3 Relationship between ejection fraction (EF) and V_m Control subjects have a normal V_m and EF three of the four patients with CMO and depressed LV function had a low V_m and EF Patients with CP had a normal EF and reduced V_{max}

both measurements so that they cluster in the lower left hand corner of the graph Patients with CP cluster to the right of the graph with a normal EF but a low V_m There was little correlation between V_m and cardiac index stroke index and LVEDP since in CP these measurements are pre determined by and reflect the severity of external compression and are less dependent on the inotropic state of the ventricle

V_m (3 element model) (Maxwell model) This method corrects for abnormal initial muscle fiber length when the end diastolic pressure is elevated When patients with CMO are compared with the control subjects the three patients with severe CMO have a much lower V_m V , and V , than the control subjects but the method does not identify one patient with mild CMO Patients with CP overlap the normal and abnormal range (Fig 4) but less discrimination is obvious when these results are compared to the assessment made using the 2 element model The 2 element model distinguishes between the three groups of patients but the Maxwell model fails to do so (Fig 5) The difference may be due to the fact that the 2 element model uses two discriminants and includes LVEDP in the comparison rather than V alone

Effect of leg raising and isoprenaline Leg raising produced a small increase or no change in peak LVdp/dt Max dp/dt/IP and in V_m (2 and 3-element models) in all three groups of patients (Table III) Isoprenaline sulfate caused an impor

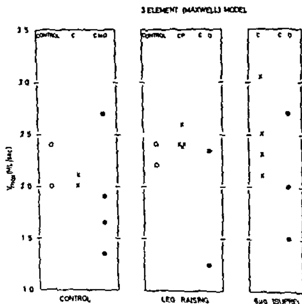


Fig 4 V calculated from a 3 element model (Maxwell model) Although V_m is reduced in three patients with CMO the groups overlap V_{max} is not altered by leg raising but increases after isoprenaline sulfate (control = control subjects CP = patients with constrictive pericarditis CMO = patients with congestive cardiomyopathy)

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Effect of pulsus paradoxus on measurements

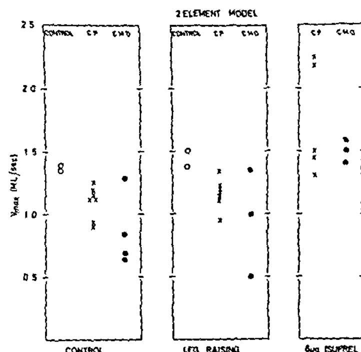


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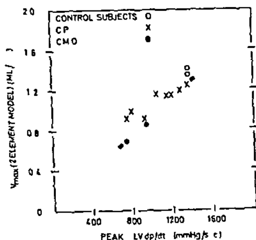


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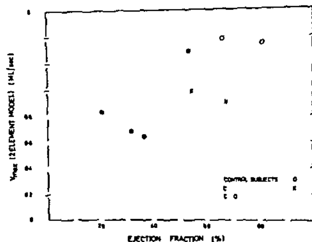


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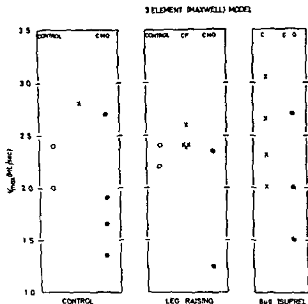


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Effect of pulsus paradoxus on measurements

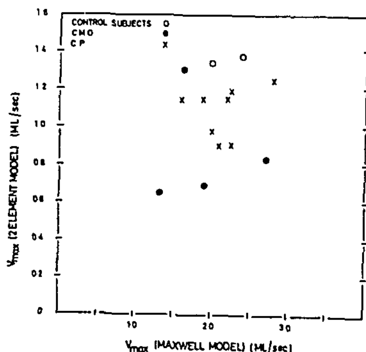


Fig 5 Comparison of V_m calculated by two methods (2 element or Hill model and 3 element Maxwell model) The 2 element model discriminates between the three groups of patients but there is no significant difference when the Maxwell model is used

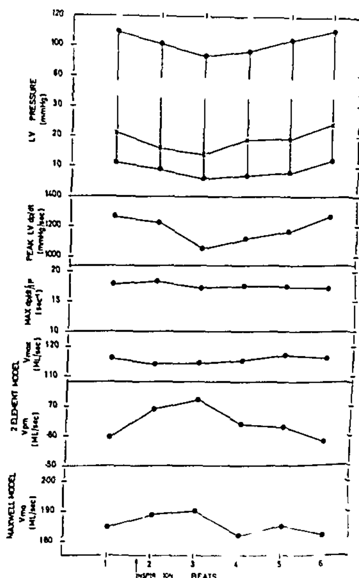


Fig 6 Effect of pulsus paradoxus on indices of ventricular celerity Peak LVdp/dt and V_m change during inspiration as a consequence of a decrease in preload There is little change in V_m (Maxwell model) and no change in V_m (2 element model) and Max dp/dt/IP This suggests that V_m (2 element model) and Max dp/dt/IP are independent of preload over a limited range

of LV celerity Fig 6 shows typical changes in measurements of LV contractility throughout a single respiratory cycle in a patient with CP (KZ) Peak LVdp/dt fell abruptly on inspiration as the LV diastolic pressures were reduced, it gradually returned to normal as the LVEDP increased There was little change in Max dp/dt/IP, but this measurement increased slightly during inspiration and it is possible that this measurement over corrected for the changes in pressure

V_m showed little change during respiration (2 and 3 element models) (Figs 6 and 7 *A* and *B*) The 3 element model may overcorrect on inspiration so that V_m was reduced in some patients as LVEDP fell and 'developed pressure increased

Vpm (peak V) varied with respiration since the point of inflexion of the force velocity curve depends on the curve itself and the LVEDP if a beat starts at a higher EDP, the ascending limb reaches the same force velocity curve at a lower V (Vpm) but at a higher load Vpm is clearly dependent on changes in LVEDP

Discussion

Velocity dependent measurements of the *mechanical function* of the left ventricle A number of indices of ventricular celerity (or velocity) have been derived from the relationship of the left ventricular pressure and its first derivative during isovolumic systole These measurements are considered to be relatively independent of preload and afterload [6, 12, 15] Recent theoretical analysis has questioned the validity of these indices,[16, 19] and this has been confirmed by experimental studies which have shown that indices which are least dependent on preload have the lowest ability to discriminate quantitatively between normality and abnormality of the contractile element [0] Further studies have challenged the validity of the uniqueness of V as an index of myocardial fiber contractility at short and at unusually long initial muscle lengths [21]

Table II Hemodynamic measurements

	MPAP (mm Hg)	LV pressure (mm Hg)			Cardiac index (L/min/M)	Stroke index (ml/beat/M)	Ejection fraction (%)
		Systolic	Early diastolic	End diastolic			
Group 1 Constrictive pericarditis							
1 D M	?6	100	16	?6	2 7	25	68
2 D M	38	117	24	40	1.9	16	88
3 M G	32	118	15	27	1 6	16	8?
4 A M	27	98	19	28	1 8	17	90
5 K. Z.	25	120	8	19	3 8	28	—
6 M K	?6	10?	5	21	2 4	29	—
7 T M	26	100	22	34	3 8	47	55
8 S M	17	118	2	13	4 3	34	70
9 V N	27	11?	19	??	3 9	35	—
Mean	27	110	14	26	2.9	27	76
1 SD	6	9	8	8	1 0	10	14
Group 2 Congestive cardiomyopathy							
10 M M	14	124	3	10	3 3	44	54
11 S C	28	112	13	35	2 8	30	21
12 A. S	30	130	5	15	?5	31	37
13 J M	31	100	16	22	1 9	31	32
Mean	2?	117	9	21	2 6	34	3?
1 SD	8	14	6	11	0 6	7	14
Group 3 Control subjects							
14 A R	13	110	2	9	2 9	26	8?
15 L. C	13	115	4	9	?6	43	67
Mean	13	113	3	9	2 8	35	75

MPAP = mean pulmonary artery pressure
Measurements in CP are the mean values over several respiratory cycles

This study compares three groups of patients control subjects patients with CMO who have a high LVEDP and a dilated left ventricle possibly due to sarcomere elongation and patients with CP who have a high EDP but a small left ventricle a consequence of external compression so that by implication the fiber length is shorter

Velocity of contractile element shortening in constrictive pericarditis and congestive cardiomyopathy comparison of the use of the 2 and 3 element models The velocity of contractile element shortening is reduced in most patients with CP—peak LVdp/dt Max dp/dt/IP and V_{max} (2 element model)—and greatly reduced in patients with CMO The 3 element (Maxwell) model corrects for the high LVEDP but the method has little value in discrimination between a normal and abnormal ventricle (e g CMO) despite its theoretical advantages and there is overlap between all three groups of patients Mehmel Krayenbuehl and Wirz also favor the use of a 2 element model for measuring V while Forman Ford and Sonnenblick[2] suggest that force velocity curves of the true contractile units would lie between the curves corrected for the Voigt and Maxwell models They calculate that any such intermediate model would produce results similar to those of the 2 element model

Peak LVdp/dt and Max dp/dt/IP correlate closely with V_m (2 element model) and are simple to calculate Although V_{max} (2 element model) is of greater discriminatory value it is questionable whether the calculation of V_m has additional practical value

The effect of pulsus paradoxus on indices of LV celerity In pulsus paradoxus there is beat to beat respiratory variation in LV diastolic pressure this is a good natural model to assess the preload dependence of the different indices of ventricular celerity Peak LVdp/dt changes abruptly on inspiration but the change in Max dp/dt/IP is small and in V_m minimal (using both 2 and 3 element models at rest and after isoprenaline) Vpm is altered by changes in LVEDP and is therefore of little value in assessing patients with an elevated LVEDP The series of force velocity curves obtained over a range of LVEDP in the same patient confirms the

Table III Measurements of contractile element velocity

		LVEDP (mm Hg)	Peak LVdp/dt (mm Hg/sec)	Max dp/dt/IP (sec)	2 element model		3 element (Maxwell) model			Mean V_{cf} (circ /sec)
					V_m	V_{pm}	V_m	V_s	V	
					(ML/sec)		(ML/sec)			
Group 1 Constrictive pericarditis										
1 D M	Control	26	740	14 2	0 90	0 48	2 10	1 75	1 50	1 38
	Leg raising	29	785	14 0	0 94	0 46	2 10	1 80	1 55	
	Isoprenaline	25	1 661	23 4	2 34	0 71	2 50	1 90	1 45	
2 D M	Control	40	1 510	15 3	–	–	2 65	2 10	1 65	2 01
	Leg raising	31	1 223	15 7	1 16	0 57	2 40	1 85	1 45	
	Isoprenaline	30	2 416	26 5	1 44	0 68	2 30	1 85	1 55	
3 M G	Control	27	1 360	17 7	1 25	0 66	2 80	2 35	2 00	–
	Leg raising	21	1 330	19 6	1.22	0 78	2 60	2 20	1 90	
	Isoprenaline	24	1 906	28 9	2.24	0 92	3 05	2 40	1 80	
4 A M	Control	28	1 162	15 7	1 15	0 54	1 60	1 35	1 20	1 87
	Leg raising	31	1 163	14 7	1 10	0 57	1 55	1 30	1 15	
	Isoprenaline	30	1 868	22 4	1 90	0 71	2 10	1 80	1 45	
5 K Z	Control	19	1 183	17 6	1 15	0 64	1 88	1 57	1 40	–
	Leg raising	19	1 155	17 9	1 13	0 67	2 17	1 93	1 68	
	Isoprenaline	21	2 084	29 6	2 19	0 97	2 00	–	–	
6 M K	Control	21	1 284	18 3	1 19	0 67	2 25	1 90	1 65	–
	Leg raising	23	1 142	17 3	1 20	0 66	2 40	1 95	1 60	
	Isoprenaline	–	–	–	–	–	–	–	–	
7 T M	Control	34	793	10 9	0 98	0 37	2 00	1 55	1 30	0 93
	Leg raising	40	846	10 9	–	–	1 70	1 45	1 30	
	Isoprenaline	29	1 661	21 4	1 30	0 71	1 85	1 60	1 45	
8 S M	Control	13	1 057	–	1 15	0 68	2 20	1 75	1 35	1 84
	Leg raising	12	1,238	–	1 34	0 77	2 35	1 90	1 60	
	Isoprenaline	12	2,356	–	1 50	1 02	2 65	2 20	1 85	
9 V N	Control	27	925	11 7	0 91	0 71	2 25	1 40	1 10	–
Mean	Control	26± 8	1 113±25	15.2±2.8	1 09±0 13	0 59±0 12	2 19±0 37	1 75+0 33	1 46±0 27	1 6±0 4
±1 SD	Leg raising	26± 9	1 110±19	15 7±2 9	1 16±0 12	0 63±0 12	2 16±0 36	1 80±0 29	1 53±0 23	
	Isoprenaline	24± 6	1 993±30	25 4±3.5	1 84±0 43	0 82±0 15	2 35±0 42	1 96±0 29	1 59±0 18	

See text for details of velocity measurements
Measurements in CP are the mean values over several respiratory cycles

early studies of Sonnenblick and colleagues[6, 12, 14] to show that over a limited range V_{max} is relatively independent of changes in preload

Pathophysiological basis for the reduction in celerity of contractile element shortening in constrictive pericarditis There are several possible explanations for a reduced velocity of contractile element shortening in CP

Is the abnormality a primary or secondary event? The relative importance of 'mechanical' and 'myocardial' factors in CP has been discussed in detail[24, 30] We believe that the primary disorder is mechanical and that the decrease in cardiac index, stroke index, and net LV stroke work index in some patients with severe constriction is a result of the Frank Starling mechanism in a small compressed underloaded ventricle[1] The reduction in diameter of myocardial fibers observed in patients with severe CP who were autopsied[31] may be a result of disuse atrophy of the fibers This mechanism may also be responsible for the reduction in the celerity of contraction under resting conditions Isoprenaline increases all measurements of LV velocity this suggests that the contractile apparatus may be basically normal and able to respond normally to an inotropic intervention

Short initial muscle length Previous studies have shown that contractile element tension and velocity in striated and in cardiac papillary

Table III Continued

	LVEDP (mm Hg)	Peak LVdp/dt (mm Hg/sec)	Max dp/dt/IP (sec)	2 element model V_m	2 element model V_{pm}	3 element (Maxwell) model V_m	3 element (Maxwell) model V	3 element (Maxwell) model V	Mean V (circ/sec)
				(ML/sec)		(ML/sec)			
Group 2 Congestive cardiomyopathy									
10 M M Control	10	1 419	16 7	1 ?9	0 8?	1 65	1 4?	1.3?	1 08
Leg raising	15	1 903	?0 0	1.35	0 90	–	–	–	
Isoprenaline	15	2 416	28 8	1 40	0 92	2 00	1 75	1 50	
11 S C Control	35	951	13 4	0 83	0 45	2 ?0	2 10	1 65	0 34
Leg raising	38	951	12 7	1 00	0 43	2.35	1 95	1 65	
Isoprenaline	9	1 872	22 3	1.57	1.27	2 70	2 40	2.20	
12. A. S Control	15	695	10 9	0 64	0 4?	1.35	1 00	0 80	0 67
Leg raising	30	725	9 7	0 50	0 35	1 ?5	1 10	1 05	
Isoprenaline	11	1 419	24 9	1 50	0 94	1.50	1 15	1 10	
13 J M Control	2?	725	10.5	0 68	0 50	1.90	1.20	1 0?	–
Mean Control	21 ± 11	948 ± 33	12 9 ± 2 9	0 86 ± 0 30	0 55 ± 0 18	1.90 ± 0 58	1 44 ± 0 48	1.21 ± 0.3?	0 ?0 ± 0 37
± 1 S D Leg raising	28	1 193	14 1	0 95	0 56	1 80	1.53	1 35	
Isoprenaline	12	1,902	25.3	1 49	1 04	2 07	1 77	1 60	
Group 3 Control subjects									
14 A. R Control	9	1,2 0	19 3	1 35	0 84	2 00	1 60	1.30	–
Leg raising	14	1 510	20 1	1 36	0 77	2.20	1.85	1 50	
15 L. C Control	9	1,270	17 4	1.38	0.90	2 40	1 75	1 25	–
Leg raising	7	1,390	18 8	1.50	1 02	2 45	2 00	1 65	
Mean Control	9	1,270	18 4	1 37	0 87	2.20	1 68	1 28	–
Leg raising	11	1 4?0	19 5	1 43	0 90	2 38	1 93	1 58	

muscle is reduced at short sarcomere lengths and two main explanations have been given

DEACTIVATION This may be an electrical phenomenon related to an interruption of the inward spread of the activating signal [32] Alternately overlapping myofilaments may directly interfere with each other's ability to produce force by a reduction in the number of cross bridge sites in parallel [33 3]

INTERNAL LOAD At short muscle lengths the overlapping actin and myosin filaments may increase the viscosity or internal resistance of the fibers to shortening [3] There may also be relengthening of a compliant element which is compressed when the fiber length is less than the slack length on relaxation (2 1 μ) and this force becomes greater during shortening

We have no data on the ultrastructure of the myocardium in constrictive pericarditis and it is not possible to study or accurately predict sarcomere length in man [3 7] We have presented the hypothetical suggestion that the muscle fibers are compressed and operate from short lengths with a concomitant fall in tension and V_m

Summary

Force velocity curves were constructed in nine patients with CP from a high fidelity LV pressure tracing and its simultaneously recorded first derivative V_m and peak V , (V_{pm}) were calculated using the 2 element (Hill) or Voigt model the curves were also constructed and V_m measured using the 3 element Maxwell model The measurements were compared with those in a group of four patients with CMO and with two control subjects Measurements of the celerity of ventricular contraction—peak LVdp/dt Max dp/dt/IP and V_m (2 element model)—were reduced in CP and greatly reduced in CMO

The effect of beat to beat variations in preload during pulsus paradoxus on the indices of ventricular celerity was studied Peak LVdp/dt and V_{pm} varied with the change in LVEDP the change in V_m was negligible using the 2 element (Hill) or Voigt model

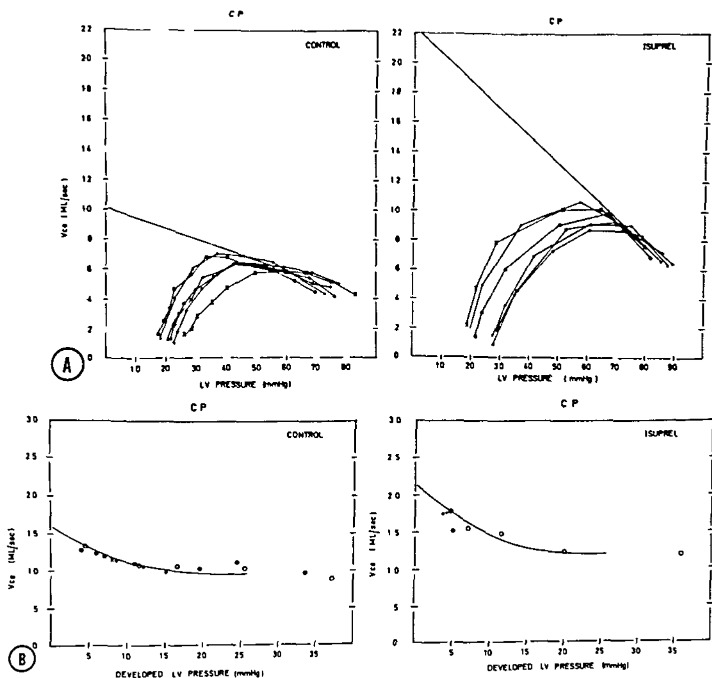


Fig 7 A Force velocity curves (constructed from the 2 element model) at rest and after intravenous isoprenaline sulfate Each curve has been constructed from a single cardiac beat and the curves represent *consecutive beats* through a single respiratory cycle Left ventricular end diastolic pressure the ascending limb of the curve and V_m (the point of inflexion) change with each beat but the descending limb and extrapolated V_m are virtually *constant* (+ = Beat 1 o = Beat 2 ● = Beat 3 • = Beat 4 O = Beat 5 × = Beat 6)

Fig 7 B Force velocity curves (Maxwell model) drawn for successive beats from a single respiratory cycle in a patient with constrictive pericarditis Each beat is represented by a different symbol Tracings are similar and the symbols have not been joined by separate lines. There is little change in extrapolated V_m The model may *overcorrect* for changes in preload and V is greatest when preload is decreased on inspiration (beat 6 after Isuprel) (after Isuprel five beats completed a respiratory cycle) A similar effect is shown in Fig 6 Symbols as in Fig 7A

The 3 *element (Maxwell)* model failed to discriminate between the three groups of patients and seems to be invalid at high LV end diastolic pressures

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Etiology of right bundle-branch block pattern after surgical closure of ventricular-septal defects

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Right bundle branch block (RBBB) after surgical closure of a ventricular septal defect (VSD) is common, but opinions differ regarding the area of damage to the conduction system Recent reports[1,2] have stated that the RBBB is caused solely by ventriculotomy and that it does not occur when the VSD is repaired through the tricuspid valve thus suggesting that RBBB after closure of VSD is due to interruption of the right ventricular subendocardial Purkinje network without injury to the main right bundle One report[1] noted a 100 per cent incidence of RBBB after vertical ventriculotomy and no RBBB in 26 cases of VSD closed through the tricuspid valve However, other reports[3-6] have implicated direct trauma—injury to or hemorrhage around the main right bundle—as the cause of the postoperative RBBB

In this study, patients with VSD were divided into two groups In one group the VSD was repaired through the tricuspid valve after atriotomy, and in the other, the VSD was repaired after ventriculotomy The incidence of postoperative RBBB in the two groups was analyzed and a tentative explanation for the site of injury to the specialized conduction tissue is given

Material and method

Choice of patient groups —Clinical records and operative notes of 424 patients with isolated VSD unassociated with complicated cardiac malformations other than atrial septal defect and patent ductus arteriosus, seen at the Mayo Clinic from January 1962 to June 1973, were reviewed, and two groups of patients were selected Group 1 patients had VSD of types 2 and 3[7] located near the membranous septum, and the VSD was repaired through the tricuspid valve after atriotomy There were 38 patients whose ages ranged from three months to 28 years with a mean of five years Group 2 patients had VSD of type 4[7] (isolated muscular VSD) repaired after ventriculotomy There were 26 patients whose ages ranged from six months to 12 years with a mean of 5 3 years

Electrocardiograms (ECG) and vectorcardiograms (VCG) —All patients had immediate preoperative and 7 day postoperative scalar ECG s taken at 50 mm per second Twenty four patients in group 1 and 12 patients in group 2 had preoperative and postoperative VCG s recorded simultaneously with the ECG on the Mayo Clinic computerized Frank vectorcardiographic system[8] All ECG s and VCG s were analyzed for the QRS duration, the mean axis of the QRS and T vectors in the frontal and horizontal planes and changes in the initial (0 02 second) and terminal (0 02 second) forces of the QRS complex Changes in the initial mean and terminal forces were evaluated by plotting the direction and magnitude of these forces in both the frontal plane (using Leads I and AVF of the ECG s and Leads X and Y of the VCG s) and in the horizontal plane (using Leads I and V_2 of the ECG s and Leads X and Z of the VCG s) The preoperative and postoperative initial, mean and terminal QRS forces of an ECG

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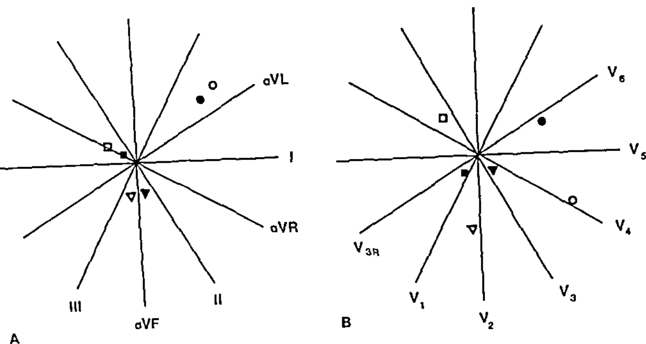


Fig 1 Immediate preoperative and seven-day postoperative scalar ECG in three year-old child who developed RBBB after repair of VSD via tricuspid valve *A* (frontal plane) and *B* (horizontal plane) show the initial forces (triangles) the mean QRS vector (circles) and the terminal forces (rectangles) reconstructed from the preoperative (open symbols) and postoperative (closed symbols) ECG There is a posterior shift of initial 0 02 ms vector (initial forces) in postoperative ECG

were plotted in the frontal and horizontal planes (example shown in Figs 1 and 2) Shifts in the position of the initial forces in the postoperative ECG s and VCG s of 3 mm (0 3 mV) or more were considered significant

The ECG and VCG criteria for diagnosis of RBBB were (1) the QRS duration exceeding age specific limits[9] (Table I) (2) rSR or Rsr' complex in Lead V_1 or V_R (or both) in the ECG s and in Lead Z in the VCG s (3) deep and slurred S waves in Lead I V_5 or V_6 of the ECG or in Lead X of the VCG and (4) terminal delay in the ECG s or VCG s characterized by a slow rate of change in the waveform of the last 0 04 to 0 02 second RBBB was diagnosed when criteria (1) and (4) and either criterion (2) or (3) were present

Hemodynamic data —The catheterization data were reviewed for the magnitude of left to right shunts (Qp/Qs) the degree of pulmonary vascular resistance (Rp) the presence of significant pulmonary hypertension (defined as pulmonary artery pressure ≥ 50 per cent of *systemic pressure*) and the presence or absence of atrial septal defect or patent ductus arteriosus

Six patients of group 1 and seven patients of group 2 had one of these associated defects In both groups 11 patients had significant pulmonary hypertension

Surgical technique —The operative notes were reviewed with particular attention to the direction of the ventriculotomy The location of the defects as visualized at surgery was noted along with the type of surgical closure of the defects that is primary suturing or patch closures Preoperative and postoperative pressure measurements were noted when available

Results

Group 1 —Two of the 38 patients had preoperative and postoperative RBBB in the ECG that did not change Of the remaining 36 patients 16 (44 per cent) had RBBB in the postoperative ECG s and available VCG s (nine VCG s) Twen*ty of the 36* patients had no significant postoperative ECG changes of these patients 15 had preoperative and postoperative VCG s that were in complete concurrence with the ECG s Initial activation judged from the position of the initial 0 02 second forces was altered in 13 of the 16

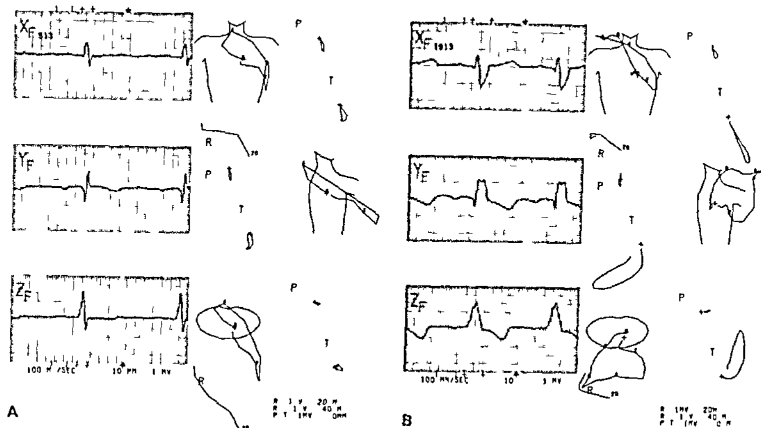


Fig 2 Immediate preoperative (*A*) and 7 day postoperative (*B*) Frank VCG in three year old child who developed RBBB after repair of VSD via tricuspid valve There is a posterior shift of initial 0 02 ms. vector in tracing with RBBB

patients with postoperative RBBB, all of whom had ECG s and eight of whom had VCG s This alteration was characterized by at least a 3 mm shift (range 3 to 8 mm) of the initial horizontal forces of the ECG or VCG posterior to the preoperative position of that portion of the ECG or VCG (Figs 1 and 2) All 20 patients without postoperative RBBB failed to show this significant 3 mm shift in initial forces in either VCG or ECG In the frontal plane changes in the initial forces occurred only in patients who developed postoperative RBBB, but the direction of these changes was not consistent All patients who developed RBBB postoperatively had inconsistent changes in the direction and magnitude of the mean and terminal QRS forces in the ECG s and available VCG's while no change in these forces occurred in patients who did not develop the RBBB pattern A consistent anterior to posterior shift of the horizontal T vector occurred in 15 of the 16 patients of group 1 who developed RBBB postoperatively (15 ECG s and nine VCG s) and in 19 of the 22 patients who did not develop RBBB (19 ECG s and 13 VCG s)

Neither the presence of significant pulmonary hypertension nor the calculated pulmonary vascular resistance nor the magnitude of the left to right shunts made any significant difference in the incidence of RBBB The incidence of RBBB in patients with patch closure of the VSD was higher than in those with primary suture closure of the VSD, but this difference was not statistically significant (Table II)

Group 2 —One of the 26 patients had preoperative and postoperative RBBB in the ECG without significant changes Fifteen of the remaining 25 patients (60 per cent) developed RBBB in the postoperative ECG and also in the VCG when available (seven VCG s) Ten patients failed to develop RBBB postoperatively absence of RBBB was demonstrated in five patients by ECG and VCG and in six by ECG only Only five of 15 patients (33 per cent) of group 2 who developed RBBB postoperatively had an anteroposterior shift of the initial forces in the horizontal plane as evident in five postoperative ECG s and in four simultaneously recorded VCG s Thus the incidence of altered initial forces in patients of group 2 was significantly lower ($P < 0.05$) than that in patients of group 1 As in group 1, changes in the mean and terminal QRS forces were evident in all ECG s and VCG s

of patients of group 2 who developed RBBB postoperatively but these changes were not in a consistent direction Initial mean and terminal forces in the ECG s and VCG s of patients who did not develop RBBB postoperatively were not altered A consistent anterior to posterior shift of the horizontal T vector occurred in all 15 patients of group 2 who developed RBBB postoperatively (15 ECG s seven VCG s) and in seven of the 11 patients who did not develop RBBB (seven ECG s five VCG s)

As in group 1 the presence of significant pulmonary hypertension the calculated pulmo nary vascular resistance and the magnitude of pulmonary blood flow did not significantly influence the incidence of RBBB in group 2 The effect of the type of the ventriculotomy incision (transverse or vertical) on the incidence of post operative RBBB could not be evaluated because the site of the incision was unknown in nine patients and was a transverse ventriculotomy in 17 Similarly the effect of primary suture closure versus patch closure on the incidence of postoper ative RBBB could not be analyzed because only one patient who developed RBBB had patch closure of the VSD

Discussion

By selecting two groups of patients with VSD s we avoided the effect of such variables as infun dibular resection on the incidence of postopera tive RBBB The defects in group 1 patients (repaired via the tricuspid valve) were types 2 and 3 VSD s in the area of the membranous septum as classified by Friedman Mehrizi and Pusch The course of the main right bundle is intimately related to the posteroinferior portion of such defects In the absence of ventriculotomy RBBB occurring postoperatively in these pa tients would most likely be due to trauma to the main right bundle Group 2 consisted of patients who underwent repair of type 4 VSD s after ventriculotomy this type of VSD is muscular and is not intimately related to the right bundle although it may be near the terminal Purkinje fibers Therefore postoperative RBBB in this group will most likely be due to interruption of the subendocardial Purkinje fibers after ventricu lotomy and not to injury of the main right bundle

Reports in the literature on the cause of the postoperative RBBB are conflicting

Table I ECG upper limits of QRS duration for diagnosis of RBBB

Age (yr)	*QRS duration (s)*
≤ 2	0 08
3 11	0 09
12 15	0 10
16+	0 12

Table II Postoperative RBBB with type of closure* of VSD in patients without ventriculot omy

	Closure	
	Primary suture (30 patients)	*Patch (8 patients)*
With RBBB	11	1
Altered initial forces		
With RBBB	8	5
Without RBBB	0	0

*No significant difference between results of suture and patch closure

While some authors believe that the ventric ulotomy alone is responsible others believe that trauma to the main right bundle near the VSD is the most likely cause Our results indicate that ventriculotomy alone is not responsible for the postoperative RBBB Otherwise the inci dence of RBBB after ventriculotomy in our study would have been 100 per cent in group 2 rather than 60 per cent only However this difference between the incidence of RBBB in our group 2 patients and that reported by Gelband and asso ciates also could be related to the direction location and size of the ventriculotomy In our patients in whom the site of the ventriculotomy was known a 61 per cent incidence of postopera tive RBBB was observed with transverse ven triculotomy (17 patients) whereas vertical ventri culotomy was used in the patients reported by Gelband and associates

Some authors believe that the nearness of the main right bundle to the VSD makes it particularly vulnerable to damage when the VSD is closed surgically The 44 per cent incidence of RBBB among our group 1 patients suggests that injury to the right bundle was responsible

Factors such as co existing atrial septal defects or patent ductus arteriosus or significant pulmo

nary hypertension did not have significant influence on the occurrence of postoperative RBBB in either group 1 or 2 In group 1 patients in whom the effect of Teflon patch versus primary suture closure was evaluated, RBBB occurred regardless of the surgical technique

Analysis of the Frank vectorcardiograms, as well as vectorial analysis of the ECG s taken at 50 mm per second rather than at 25 mm per second, made it possible to differentiate central right bundle injury from distal Purkinje fiber injury Central injury most likely will affect both the initial and terminal forces whereas peripheral fiber injury will alter the terminal forces only Eighty one per cent of group 1 and only 33 per cent of group 2 patients showed an anterior to posterior shift of the initial forces (Fig 2) in the presence of RBBB This observation agrees with that of Scherlis and Lee,[14] who noted no change in the duration of the initial one third of the horizontal QRS loop but noted a shift in the overall loop leftward and posteriorly in postoperative RBBB after repair of membranous VSD s We assume that alteration in the initial forces in RBBB *results from an injury to the specialized* conduction tissue to the septum which is more likely to occur with membranous VSD The lower incidence of changes in the initial forces in group 2 patients (with muscular VSD) can be explained by the less close relationship of the VSD and the specialized conduction tissue While the incidence of altered initial forces was statistically different in the two groups of patients who developed RBBB postoperatively, our data do not suggest that the cause of postoperative RBBB can be elucidated from the ECG or VCG in an individual patient

Summary

An incidence of 60 per cent of postoperative RBBB in the ECG s and available VCG's of 26 patients with isolated muscular VSD repaired was noted after ventriculotomy In the 38 patients with VSD s near the membranous septum who underwent repair via the tricuspid valve the incidence of postoperative RBBB was 44 per cent Results suggested that either ventriculotomy or injury to the right bundle near the VSD can cause RBBB after surgical closure of the defect Changes in the initial 0 02 second electrovectorcardiographic forces in patients with postoperative RBBB were thought to result from central injury to the specialized conduction tissue supplying the interventricular septum Peripheral RBBB, therefore, could be separated from central RBBB by the appearance of the initial electro vectorcardiographic forces For detection of these *changes in initial forces, both the ECG recorded* at 50 mm per second and the Frank VCG were useful

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Quinidine plasma concentration and exertional arrhythmia

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Frequent complex arrhythmia occurring during and shortly after maximal exercise testing is a frequent finding in asymptomatic individuals and those with symptomatic heart disease Repeated testing with a single oral dose of Pronestyl (pro cainamide) showed a definite relationship of premature contraction suppression to plasma concentration in individuals with frequent ar rhythmia and also that some individuals are refractory to treatment regardless of plasma concentration We studied oral quinidine to define its therapeutic role and to determine its hemodynamic and electrocardiographic effects in individuals with frequent premature contrac tions

Materials and methods

Subjects identified through the Seattle Heart Watch as having frequent arrhythmia (more than ten abnormal premature beats) during and after maximal treadmill exercise were entered into the study There were 29 subjects (27 men average age 53 5 years range 35 to 67 two women 26 and 67 years) Sixteen subjects had cardiovascular disease including three with hypertension and 13 with symptomatic coronary disease Another 12 were considered healthy One individual studied had Wolf Parkinson White syndrome

After giving informed consent all subjects had a routine maximal treadmill exercise test A continuous bipolar CB, electrocardiogram (ECG) was simultaneously recorded on paper at 25 mm per second and on magnetic tape for off line computer analysis of ST segment changes during rest exercise and recovery using methods previously described[3] Arrhythmia was edited from this analysis ST_B 50 to 69 msec after nadir of S was measured at rest maximum exercise 0 recovery three minutes and five minutes into the recovery period

The number of abnormal beats occurring dur ing exercise and the immediate ten minute recovery period were counted and classified using standard ECG criteria A severity score was given to the complexity of arrhythmia and the sum of this score represented the Severity Index [*2]

Both the number and the Severity Index were calculated for the control exercise test and for the two hour test with oral quinidine Blood pres sures at rest exercise and recovery were meas ured with auscultation and sphygmomanometry The heart rate was calculated from the ECG Samples of expired air were collected during the last few minutes of exercise to determine maximal oxygen consumption using standard ized techniques Serum potassium urea nitrogen and creatinine were determined in most of the subjects Mean values were K = 4 1 ± 0 49 mEq per liter (3 2 to 5 2 mEq per liter) 30 determinations blood urea nitrogen = 16 2 ± 4 2

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*Scori g f arrhythmia by sev rity 1 = s gle prematu e atrial r ventricula be t 2 = two or m re premat re beats including b gem iny fusion r berrant onduct o or all 3 = R-on T phenomenon (premature v tricular be t occurring on preceding T wa) coupled premature beats, trial fibrill t on and mult focal v ntricular beats 4 = three more premat re ventricular be ts in a row (ventricular tachycardia)

nary hypertension did not have significant influence on the occurrence of postoperative RBBB in either group 1 or 2 In group 1 patients in whom the effect of Teflon patch versus primary suture closure was evaluated RBBB occurred regardless of the surgical technique

Analysis of the Frank vectorcardiograms, as well as vectorial analysis of the ECG's taken at 50 mm per second rather than at 25 mm per second made it possible to differentiate central right bundle injury from distal Purkinje fiber injury Central injury most likely will affect both the initial and terminal forces, whereas peripheral fiber injury will alter the terminal forces only Eighty one per cent of group 1 and only 33 per cent of group 2 patients showed an anterior to posterior shift of the initial forces (Fig 2) in the presence of RBBB This observation agrees with that of Scherlis and Lee,[14] who noted no change in the duration of the initial one third of the horizontal QRS loop but noted a shift in the overall loop leftward and posteriorly in postoperative RBBB after repair of membranous VSD s We assume that alteration in the initial forces in RBBB results from an injury to the specialized conduction tissue to the septum, which is more likely to occur with membranous VSD The lower incidence of changes in the initial forces in group 2 patients (with muscular VSD) can be explained by the less close relationship of the VSD and the specialized conduction tissue While the incidence of altered initial forces was statistically different in the two groups of patients who developed RBBB postoperatively our data do not suggest that the cause of postoperative RBBB can be elucidated from the ECG or VCG in an individual patient

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Table II Effect of different doses of quinidine on frequency and severity of arrhythmia

	Subject No	Control		2 hour		Plasma level (μg/ml)
		Freq	Sev	Freq	Sev	
5 mg /Kg						
Successful ↓ Freq 100% Sev 100%	36	445	18	0	0	0.96
Partially successful ↓ Freq ≥ 88% Sev ≥ 53%	43	91	17	2	4	0 82
Unsuccessful Freq < 88% Sev < 53%	40	131	20	4?	7	0 61
	28	125	8	9	4	1 04
	42	46	8	9	10	0 98
10 mg /kg						
Successful ↓ Freq 100% Sev 100%	?8	121	6	0	0	1.89
	42	47	12	0	0	1 49
	37	31	5	0	0	2 07
	4	32	10	0	0	1 61
	5	28	10	0	0	1 49
Partially successful ↓ Freq ≥ 76% Sev ≥ 51%	43	98	11	15	4	1 6?
	3	537	12	11	4	1 65
	31	442	14	40	4	1.55
	40	94	12	25	5	1 17
	41	45	11	30	12	1.54
	36	6?0	20	7	1?	2 11
	20	361	19	249	9	1.83
Unsuccessful Freq < 76% Sev < 51%	1	113	19	63	19	1 40
	6	106	12	3	10	2 02
	32	61	2	30	2	1 63
	27	348	1?	114	19	2 31
	19	219	19	31	10	1 64
	38	10	12	3	10	1 13
	39	321	5	291	5	1 75
15 mg /kg						
Successful ↓ Freq 100% Sev 100%	33	166	15	0	0	2 87
	3	621	15	0	0	2 31
	34	20	7	0	0	2 45
Partially successful ↓ Freq ≥ 75% Sev ≥ 59%						
Unsuccessful Freq < 75% Sev < 59%	1	139	19	65	10	1 71
	15	220	16	29	13	2 59
	13	119	15	56	13	1 70
	20	374	19	271	12	2 88

Average per cent reduction from cont ol te t figure ↓
Abbreviations Freq, frequency Sev Se erity Inde ↓ supp ess on

were two in whom there was slight improvement and two in whom the higher dose was possibly toxic One of these (No 41) denied having taken quinidine within 25 hours of his second test Nevertheless he was found to have a quinidine plasma level of 0 56 μg per milliliter at the start of the second control test (24 hours after the first) At the 5 mg per kilogram dose his premature contractions were better suppressed than at the 10 mg per kilogram dose but in view of the presence of residual plasma quinidine he was not considered representative and his data were not included in the analysis

Plasma concentration with time Fig 1 shows the average plasma levels at three doses 5 mg per kilogram 10 mg per kilogram and 15 mg per kilogram Generally, there is a linear plasma level-dose relationship but with the plasma levels remaining relatively stable between the first and the second hour A decrease in the standard devi

Table I Responses to exercise tests *with* and without oral quinidine (10 mg per kilogram), control test (without drug), *test 2 hours later (with drug)*

	Dur	V m	Freq	Resting			Maximum		Mean plasma level
				Sev	*HR*	*SBP*	*HR*	*SBP*	(μg/ml)
n	19	17	19	19	19	19	19	19	19
Mean (control)	513	31 3	191	12	68	127	167	181	1 68
(2 hrs)	*491*	*31 0*	*48*	*6 58*	*82*	*115*	*167*	*142*	
S D	± 141	± 7 87	± 189	± 5 3	± 11 9	± 15 8	± 14	± 24	± 0 31
	± 125	*± 7 97*	*± 84*	*± 6 1*	*± 15 8*	*± 13 9*	*± 15*	*± 22*	
t	2 729		3 512	5 533	3 693	5 035		5 846	S E M = 0 070
P	0 0137	NS	0 0025	0 00001	0 0017	0 0001	NS	0 00001	

Abbreviations DBP SBP diastolic systolic blood pressure Dur duration of test Freq frequency of arrhythmia Max maximal exercise Sev Severity Index V̇ m maximal oxygen uptake in milliliters per (kilogram minute)

mg per 100 ml (6 to 26 mg per 100 ml), 27 determinations, and creatinine = 1 2 ± 0 22 mg per 100 mg (0 6 to 1 6 mg per 100 ml) 25 determinations

Immediately after the routine control test, 19 subjects were given oral quinidine gluconate (10 mg per kilogram) Two hours later the same exercise test was repeated Blood samples were collected at 30 60 90 and 120 minutes and after the second exercise test for the measurement of plasma concentration of quinidine using the method of Cramer and Isaaksson [5]

Results

The responses to the two tests are shown in Table I and include duration of multistage test, maximal oxygen uptake ($V_{O_{max}}$) arrhythmia frequency and severity heart rate systolic blood pressure at rest and at maximum working capacity and the mean of the plasma levels taken before and at the end of the two hour test Over all significant decreases in frequency and severity of arrhythmia were recorded during the two hour test There was a significant fall in systolic blood pressure at rest and at maximum a small but significant decrease in duration of exercise, and an increase in resting heart rate no significant difference in $V_{O_{2max}}$ and maximal heart rate could be found The mean plasma concentration was 1 68 μg per milliliter which is a therapeutic plasma level [4]

Clinical effectiveness It was not possible to establish a plasma level response relationship because of the small number of patients used Consequently, therapeutic effectiveness could only be evaluated on an individual basis For example there were five individuals whose premature contractions were completely eliminated but there were three individuals in whom arrhythmia reduction was only partial Not all these differences could be accounted for by differences in plasma level (Table II) It is highly suggestive that in the majority of the subjects tested at the 10 mg per kilogram dose quinidine was unsuccessful in reducing arrhythmia induced with maximal exercise despite therapeutic plasma concentrations of the drug Treatment was considered one hundred per cent successful when the premature contractions were completely suppressed at the two hour test Treatment was considered partially successful when reduction of both frequency and severity of the premature contractions exceeded the average for the group for this dose level, but was less than 100 per cent Treatment was considered unsuccessful when the reduction in either frequency or severity was less than the average

Table II also shows similar distributions and average reductions in frequency and Severity Index when a 5 mg per kilogram and a 15 mg per kilogram dose is used with the same testing protocol (Not all subjects were started on the 10 mg per kilogram dose as in our former [Pronestyl] study)

Individual responses to dose adjustment Table III shows ten individuals who were tested at two different dose levels Four of the ten individuals improved with a higher dose There

symptomatic disease Changes for better or worse could not be attributed to the dose level

Reproducibility Subjects who were tested at two or more dose levels did a control test before each A comparison of the control tests conducted by the same investigators sometimes weeks apart (90 ± 132 days range 1 to 420 days) was made in order to test the reproducibility of the responses in this group of subjects The paired *t* test revealed no significant differences in any of the parameters tested These were heart rate blood pressure prevalence of premature contractions Severity Index duration of test V_{O_m} and ST_B computer values at rest maximum and in the immediate recovery period

Discussion

The present study was done to record the effects of a single oral dose of quinidine gluconate given as a measured solution of a commercially available product on the frequency and severity of arrhythmia occurring with maximal treadmill exercise testing On the average quinidine successfully reduced both frequency and severity The mean plasma concentration at the time of the second test was in the therapeutic range (1 to 4 µg per milliliter) However there were individuals in whom the drug was not successful despite therapeutic levels Raising the dose was helpful to some but not all of these subjects This agrees with the recent clinical findings of Jelinek Lohrbauer and Lown[5] The effect of quinidine was not compared with the effect of a placebo which would have taken into consideration the changes in resting heart rate from the control test to the two hour test These could be considered in future studies

Quinidine has a relatively long biological half life (6 to 8 hours) and it was therefore not practicable to perform a third exercise test (on the same day) to determine whether a decrease in plasma concentration is accompanied by a corresponding increase in arrhythmia frequency and severity as was found in our studies with procainamide

Toxic side effects chiefly subsequent malaise and diarrhea were common occurrences at the two higher doses Minor but significant changes occurred in resting heart rate and blood pressure but we did not find hypotension or syncope to be problems

Computer measured S T changes after treatment with the drug were not significant This was not the case with Pronestyl[2] which caused a significant decrease in the maximal ST_B value

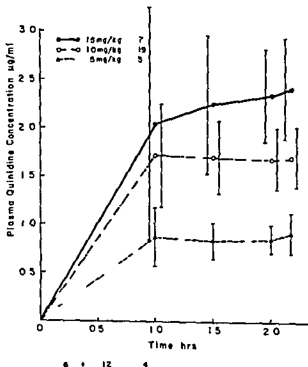


Fig 1 Differences in all mean values $P < 0.01$ except for one hour values at 10 and 15 mg per kilogram $P < 0.05$

Because he had experienced ventricular tachycardia in the control test one subject (No 35) who was on a digoxin regimen was tested three times His digoxin plasma level at that time was 2 2 ng per milliliter His digoxin was decreased and he was exercised again several weeks later this time with oral quinidine (10 ml per kilogram) and again he developed sustained ventricular tachycardia despite the quinidine The plasma digoxin level this time was 1 1 ng per milliliter and the quinidine level 2 61 µg per milliliter Several weeks later off digoxin but using the same dose of quinidine he did not develop ventricular tachycardia when retested His digoxin level had dropped to zero and his plasma quinidine concentration was 2 63 µg per milliliter To this subject who was at risk of serious arrhythmia digoxin could clearly be considered toxic at usual clinical therapeutic levels and his ventricular tachycardia in the presence of digoxin was unaffected by a therapeutic plasma level of quinidine Without the digoxin quinidine was successful

Table III Patients tested at two doses of quinidine

Patient No	Dose (mg /kg)	Arrhythmia changes		Plasma level at test [μg/ml (average)]	Comment
		Freq (%)	Sev (%)		
36	5	−100	−100	0 96	Successful
	10	−99	−40	2 12	(Toxic?)
40	5	−68	−65	0 61	Beneficial
	10	−73	−58	1 18	Unsuccessful
41	5	−98	−88	1 42	(See text)
	10	−33	0	1 54	
42	5	−80	+25	0 98	Unsuccessful
	10	−100	−100	1 49	Successful
43	5	−98	−76	0 82	Beneficial
	10	−89	−73	1 62	Beneficial
28	5	−93	−50	1 04	Beneficial
	10	−100	−100	1 89	Successful
1	10	−44	0	1 40	Unsuccessful
	15	−55	−47	1 71	Beneficial
3	10	−98	−67	1 65	Beneficial
	15	−100	−100	2 31	Successful
20	10	−31	−53	1 63	Beneficial
	15	−28	−37	2 88	Unsuccessful
33	7 5	−50	−73	1 45	Beneficial
	15	−100	−100	2 87	Successful

† = μg/ml

Abbreviations Freq frequency Sev Severity Index

Table IV ST_B responses before and after oral quinidine (10 mg /kg)

	Rest		Stage I		Max		0 Recovery		3 hours		5 hours	
	Control	2 hour	Control	2 hour	Control	2 hour	Control	2 hour	Control	2 hour	Control	2 hour
Mean	0 051	0 033	−0 026	−0 007	−0 139	−0 123	−0 043	−0 059	−0 074	−0 050	−0 072	−0 043
S D	±0 014	±0 038	±0 090	±0 059	±0 078	±0 069	±0 054	±0 089	±0 131	±0 107	±0 152	±0 047

n = 14 No significant differences by paired t tests between control and 2 hour values

1 7 m p h 10 per cent gradient

ation after taking the one hour blood sample was also noted which suggests some type of steady state between absorption and elimination

ST_B analysis by computer ST_B responses of 14 of the subjects were analyzed by computer before and after the 10 mg per kilogram dose of quini dine Editing out of the premature contractions before computer analysis was done off line No significant differences could be found between the control and two hour values at any stage of the tests The results are shown in Table IV

Relationship of change in plasma concentra tion to change in hemodynamic measurements at maximum exertion The plasma concentration at two hours and the change from the control to the two hour test in maximum heart rate (plasma concentration = ΔHR × 4 7 – 7 39, r = 0 39) and maximum systolic blood pressure (ΔSBP_m × 0 50 – 32 7 r = 0 011) were evaluated for 27 of the subjects tested, irrespective of oral dosage but no significant correlation could be found

The postexercise assessment of each subject in this study was evaluated, using the standard Seattle Heart Watch form for exercise testing evaluation to classify the individual according to the number of normal questionable and abnor mal hemodynamic parameters symptoms physi cal signs and electrocardiographic changes noted with maximal exercise Each subject was also classified according to clinical diagnosis of heart disease—inapparent possible probable or defi nite — based on the history, physical examination and resting 12 lead ECG findings Over all oral quinidine did not change the final exercise classi fications of the healthy asymptomatic individu als Over all the same was true for patients with

symptomatic disease Changes for better or worse could not be attributed to the dose level

Reproducibility Subjects who were tested at two or more dose levels did a control test before each. A comparison of the control tests conducted by the same investigators sometimes weeks apart (90 ± 132 days range 1 to 420 days) was made in order to test the reproducibility of the responses in this group of subjects The paired *t* test revealed no significant differences in any of the parameters tested These were heart rate blood pressure prevalence of premature contractions Severity Index duration of test $V_{O_{2m}}$ and ST_B computer values at rest maximum and in the immediate recovery period

Discussion

The present study was done to record the effects of a single oral dose of quinidine gluconate given as a measured solution of a commercially available product on the frequency and severity of arrhythmia occurring with maximal treadmill exercise testing On the average quinidine successfully reduced both frequency and severity The mean plasma concentration at the time of the second test was in the therapeutic range (1 to 4 µg per milliliter) However there were individuals in whom the drug was not successful despite therapeutic levels Raising the dose was helpful to some but not all of these subjects This agrees with the recent clinical findings of Jelinek Lohrbauer and Lown [6] The effect of quinidine was not compared with the effect of a placebo which would have taken into consideration the changes in resting heart rate from the control test to the two-hour test These could be considered in future studies

Quinidine has a relatively long biological half life (6 to 8 hours) and it was therefore not practicable to perform a third exercise test (on the same day) to determine whether a decrease in plasma concentration is accompanied by a corresponding increase in arrhythmia frequency and severity as was found in our studies with procainamide [2]

Toxic side effects chiefly subsequent malaise and diarrhea were common occurrences at the two higher doses Minor but significant changes occurred in resting heart rate and blood pressure but we did not find hypotension or syncope to be problems

Computer measured S T changes after treatment with the drug were not significant This was not the case with Pronestyl [2] which caused a significant decrease in the maximal ST_B value

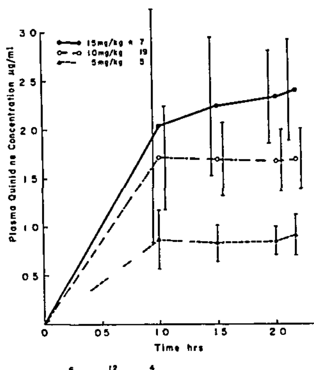


Fig 1 Differences in all mean values $P < 0.01$ except for one-hour values at 10 and 15 mg per kilogram $P < 0.05$

Because he had experienced ventricular tachycardia in the control test one subject (No 35) who was on a digoxin regimen was tested three times His digoxin plasma level at that time was 2 2 ng per milliliter His digoxin was decreased and he was exercised again several weeks later this time with oral quinidine (10 ml per kilogram) and again he developed sustained ventricular tachycardia despite the quinidine The plasma digoxin level this time was 1 1 ng per milliliter and the quinidine level 2 61 µg per milliliter Several weeks later off digoxin but using the same dose of quinidine he did not develop ventricular tachycardia when retested His digoxin level had dropped to zero and his plasma quinidine concentration was 2 63 µg per milliliter To this subject who was at risk of serious arrhythmia digoxin could clearly be considered toxic at usual clinical therapeutic levels and his ventricular tachycardia in the presence of digoxin was unaffected by a therapeutic plasma level of quinidine Without the digoxin quinidine was successful.

The patient with Wolf Parkinson White syndrome was considered separately She showed 77 per cent reduction in arrhythmia frequency and 50 per cent reduction in severity Her response was no different from that of the rest of the subjects studied

Conclusions

Quinidine gluconate given in a single oral dose (10 mg per kilogram) appears to be somewhat beneficial in the suppression of premature contractions In a small percentage of persons with frequent premature contractions, it is completely successful In an equal number, the higher dose (15 mg per kilogram) is completely successful in others the benefit is only partial

It is not possible to predict in whom the drug will be successful nor in whom the mild toxic effects will occur

Summary

Quinidine gluconate was used to treat arrhythmia induced with maximal exercise testing Twenty nine subjects who had previously developed frequent premature contractions on testing were selected for further study After a control maximal exercise test, quinidine (10 mg per kilogram) in solution was given orally in a single dose and two hours later the same test was repeated Recurrence of premature contractions was completely prevented in five of the 19 subjects tested, suppression was better than the mean value in three others and in 11 subjects it was below the mean value The plasma concentration at two hours was 1 68 ± 0 31 μg per milliliter which is a therapeutic level

Raising the dose to 15 mg per kilogram eliminated the premature contractions in six subjects whose response to 10 mg per kilogram had not been complete but not in two others Lowering the dose to 5 mg per kilogram lowered the plasma level to below the therapeutic level

No differences between the responses to the drug of the otherwise healthy subjects and those with symptomatic heart disease could be found

Compared with the responses to the control tests, there were small but significant changes in the second test in heart rates blood pressure and duration of exercise Aerobic working capacity estimated by $V_{O_{max}}$ was unchanged

Mild toxic effects manifested by malaise and diarrhea were a common finding with both 10 mg per kilogram and 15 mg per kilogram of quinidine but not with 5 mg per kilogram

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Electrophysiologic effects of isoproterenol on cardiac conduction system in man

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The effects of sympathomimetic drugs on the electrophysiologic properties of the cardiac conduction system have been the subject of previous studies.[1-3] It is well accepted that these agents accelerate sinus rate, enhance A-V nodal conduction, and increase the discharge rate of idioventricular pacemakers. Some controversy exists regarding effects of isoproterenol (ISOP) on the His-Purkinje system. Previous studies in isolated animal preparations and intact human hearts[5] indicate that isoproterenol has no appreciable influence on His-Purkinje conduction. However, in a recent study, it was reported that isoproterenol consistently facilitated His-Purkinje conduction in patients with either normal or prolonged control values as evidenced by a decrease in the H-V interval following drug administration.

Electrophysiologic studies were performed in 16 patients utilizing His bundle electrograms and the effects of isoproterenol on atrioventricular conduction and refractoriness were evaluated. The well known effects of isoproterenol on sinus rate and A-V nodal conduction were consistently observed. Isoproterenol in the doses infused (1 mcg. per minute) did not appear to have any effect on His-Purkinje conduction time. The purpose of this report is to present results obtained in these patients and to discuss some of the reasons which might explain existing discrepancies.

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Materials and methods

Right heart catheterization was performed in 16 patients in the postabsorptive nonsedated state. The nature of the study was explained and a signed consent was obtained. Bundle of His electrograms were recorded as previously described using a tripolar electrode catheter which was percutaneously introduced into the right femoral vein and fluoroscopically positioned in the region of the tricuspid valve.[9] A quadripolar electrode catheter was percutaneously introduced into an antecubital vein and advanced to the high right atrium near its junction with the superior vena cava. The distal two electrodes were used to stimulate the right atrium and the proximal two electrodes used to record a high right atrial electrogram. Intracardiac electrograms as well as electrocardiographic Leads I, II, III, and V_1 and time lines generated at 10 and 100 msec. were simultaneously displayed on a multichannel oscilloscope and relayed to a magnetic tape recorder. The records were subsequently reproduced at paper speeds of 150 and 200 mm. per second. Electrical stimulation was accomplished using a programmed digital stimulator which delivered impulses of 1.5 msec. at approximately twice diastolic threshold. The functional properties of the A-V conduction system were determined at one or more basic atrial cycle lengths using the atrial extrastimulus method.[9, 11] The right atrium was stimulated at a predetermined basic cycle length (A_1A_1) and following every eight basic drive beat a premature atrial impulse (A_2) was introduced at progressively decreasing A_1A_2 intervals to the point of atrial refractoriness. Careful attention was paid to the grounding of all equipment. After completing the control studies isoproterenol was given by continuous intrave-

Table 1 Clinical data and A V conduction during sinus rhythm before and after isoproterenol

No	Age	Sex	Diagnosis	Resting ECG	Sinus cycle length (msec)		A H interval (msec)		H V interval (msec)	
					Before	*After*	*Before*	*After*	*Before*	*After*
1	65	M	Systemic hypertension	Normal	1 100	870	125	92	52	52
2	59	M	Systemic hypertension	Normal	1 060	615	112	102	48	48
3	65	M	ASHD	RBBB + LAD	795	720	100	92	52	52
4	81	M	ASHD	RBBB + LAD First degree A V block	780	565	135	125	90	90
5	42	M	NHD	Normal	940	700	118	105	40	40
6	52	M	ASHD	RBBB + LAD	1 025	890	85	58	38	38
7	56	M	ASHD	Normal	940	665	75	65	40	40
8	52	F	NHD	Normal	610	490	110	95	58	58
9	39	M	NHD	Normal	910	795	95	90	45	45
10	53	M	ASHD	RBBB	900	570	75	65	40	40
11	57	M	ASHD	Normal	635	395	70	45	32	32
12	61	M	ASHD	Sinus bradycardia	1 200	715	70	60	50	50
13	32	M	Systemic hypertension	Normal	830	630	95	70	60	60
14	62	F	Systemic hypertension	Normal	1 100	800	100	70	40	40
15	54	M	Systemic hypertension	LBBB	850	710	120	105	50	50
16	59	M	ASHD	LBBB	820	530	85	60	80	80
			Mean		*906 ± 165*	*666 ± 136*	*98 ± 20*	*80 ± 22*		
			P value		P < 0 001		P < 0 001			

ASHD atherosclerotic heart disease NHD no heart disease LAD left axis deviation of more than −30 LBBB left bundle branch block and RBBB right bundle branch block

nous infusion (microdrops), and electrophysiologic measurements were repeated ten minutes after the infusion was stabilized at the desired rate of 1 mcg per minute The procedure was well tolerated and no adverse effects were noted

Definition of terms *Antegrade conduction A H interval* was used as an approximation of A V nodal conduction time and was measured from the onset of the low atrial electrogram to the onset of the His bundle electrogram (normal values for our laboratory, 60 to 140 msec) *H V interval* represented conduction time within the His Purkinje system and was measured from the onset of the His bundle deflection to the earliest onset of ventricular activity as noted either on the ECG or HBE tracing (normal values for our laboratory, 30 to 55 msec)

Antegrade refractory periods ' A_1 H_1 and V_1 represents atrial His bundle, and ventricular depolarizations of the basic atrial drive A_2 H_2 and V_2 represent atrial, His bundle and ventricular depolarizations of the premature atrial beats *Effective refractory period (ERP)* of the atrium is defined as the longest S_1S_2 interval at which S_2 fails to depolarize the atrium, S representing the stimulus artifact *ERP of the AVN* is defined as the longest A_1A_2 interval at which A_2 fails to propagate to the His Purkinje system (HPS) *Functional refractory period (FRP)* of the AVN is defined as the shortest H_1H_2 interval that results from any A_1A_2 *ERP of the HPS* is defined as the longest H_1H_2 interval at which H_2 fails to conduct to the ventricles *Relative refractory period (RRP) of the HPS* is generally defined as the longest H_1H_2 interval at which H_2 conducts to the ventricles with a longer H V interval than the basic drive beat or results in an aberrant QRS complex However the detection of minor degrees of aberrant ventricular conduction was more difficult to determine and was subject to greater observer error Therefore for the purpose of this study the longest H_1H_2 interval resulting in definite bundle branch block pattern QRS axis shifts of more than 30° in the frontal plane or H V prolongation was taken as the RRP of the HPS Although it is recognized that the HPS is a trifascicular system in the absence of multiple recording sites along individual fascicles it is

Table II Antegrade refractory period data

Patient No	Atrial cycle length	Atrium ERP		A V node				His Purkinje system RRP	
				FRP		ERP			
		B fore	After	Before	After	Before	After	Before	After
1	700	310	300	475	375	380	< 300		425
	600	300	290	460	350	390	< ?90		430
	500	?,0	260	470	340	400	< ?60		425
2	600	300	260	380	335	< 300	< ?60		
	500	250	260	355	330	< 250	< 260		
3	600	? 0	290	345	345	< ?"0	< ?90		
	500	270	250	350	330	300	280		
[illegible]	600	260	240	545	375	450	260		370
	650	270	240	570	3,0	500	< ?40		395
6	600	230	260	445	370	330	< 260		
	550	260	250	440	380	335	< 250		
7	,00	290	250	390	350	< 290	< 250	400	385
	600	?70	250	360	350	< 2"0	< 250	365	355
	500	250	230	3ɔ5	340	270	< 230	430	4?0
8	450	240	230	445	380	300	230		
9	600	270	260	415	355	340	< 260		
	500	250	260	400	340	340	< 260		
10	700	?40	250	430	365	3 0	280		385
	550	40	250	350	330	< 240	< 250		330
	500	220	250	450	315	400	260		325
11	550	2?0	210	330	315	< 220	< ?10	3ɔ5	345
	500	2?0	230	320	305	< 2?0	< ?30	335	3?0
	450	230	230	315	300	< 230	< 230		
12	700	2 0	230	410	345	< 2,0	< 230	480	475
	600	270	230	395	3?0	290	< 230	465	455
13	600	250	2?0	395	350	280	< 220	400	385
	500	2?0	210	385	315	280	< 210	430	420
14	700	2"0	240	510	410	3 0	< 240	535	5?5
	600	?60	2?0	490	350	3,0	< 220	530	520
	500	2?0	210	465	330	400	2 0	480	4,0

All alues (oth tha patient number) are in milliseconds
In p tients Nos 4 15 a d 16 o ref actory period tudies wer performed

impossible to measure the ERP versus the RRP of any given fascicle Thus for the purposes of this study it was elected to consider the HPS as a single functioning unit

Results

The essential clinical and electrophysiologic data are presented in Tables I and II None of the patients were taking any cardioactive medica tions at the time of the study Fifteen patients had P R intervals of normal duration and one patient (No 4 Table I) had first degree A V block with a wide QRS complex

Sinus cycle length In all patients ISOP resulted in sinus acceleration (Fig 1) The average decrease in sinus cycle length was 240 msec p value <0 001 (Table I) The mean sinus cycle length measured 906 msec ±165 msec during the control period and 666 msec ±136 msec following isoproterenol administration

Antegrade conduction studies (Table I) *A V node* ISOP facilitated A V nodal conduction as indicated by a shortening of A H intervals during sinus rhythm (16 patients) and at various paced atrial rates (14 patients) The average decrease in A H interval during sinus rhythm was 17 msec (range 5 to 33 msec) p value <0 001 The short ening of A H intervals after ISOP was more pro nounced at the faster paced atrial rates For example in 14 patients who demonstrated a 1 1 atrioventricular response at a paced atrial cycle length of 500 msec (heart rate of 120 per minute) the average decrease in A H interval following isoproterenol was 62 msec (range 18 to 210 msec) p value <0 001 Furthermore in 12 patients the onset of A V nodal Wenckebach type

Table I Clinical data and A V conduction during sinus rhythm before and after isoproterenol

No	Age	Sex	Diagnosis	Resting ECG	*Sinus cycle length (msec)*		*A H interval (msec)*		*H V interval (msec)*	
					Before	*After*	*Before*	*After*	*Before*	*After*
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6	52	M	ASHD	RBBB + LAD	1 025	890	85	58	38	38
7	56	M	ASHD	Normal	910	665	75	65	40	40
8	52	F	NHD	Normal	610	490	110	95	58	58
9	39	M	NHD	Normal	910	795	95	90	45	45
10	53	M	ASHD	RBBB	900	570	75	65	40	40
11	57	M	ASHD	Normal	635	395	70	45	32	32
12	61	M	ASHD	Sinus bradycardia	1 200	715	70	60	50	50
13	32	M	Systemic hypertension	Normal	830	630	95	70	60	60
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15	54	M	Systemic hypertension	LBBB	850	710	120	105	50	50
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Antegrade refractory periods[12] A_1 H_1 and V_1 represents atrial His bundle, and ventricular depolarizations of the basic atrial drive A_2, H_2 and V_2 represent atrial His bundle and ventricular depolarizations of the premature atrial beats *Effective refractory period (ERP)* of the atrium is defined as the longest S_1S_2 interval at which S_2 fails to depolarize the atrium, S representing the stimulus artifact *ERP of the AVN* is defined as the longest A_1A_2 interval at which A fails to propagate to the His Purkinje system (HPS) *Functional refractory period (FRP)* of the AVN is defined as the shortest H_1H interval that results from any A_1A *ERP* of the *HPS* is defined as the longest H_1H_2 interval at which H fails to conduct to the ventricles *Relative refractory period (RRP) of the HPS* is generally defined as the longest H_1H_2 interval at which H_2 conducts to the ventricles with a longer H V interval than the basic drive beat or results in an aberrant QRS complex However, the detection of minor degrees of aberrant ventricular conduction was more difficult to determine and was subject to greater observer error Therefore for the purpose of this study the longest H_1H_2 interval resulting in definite bundle branch block pattern QRS axis shifts of more than 30° in the frontal plane or H V prolongation was taken as the RRP of the HPS Although it is recognized that the HPS is a trifascicular system in the absence of multiple recording sites along individual fascicles it is

the atrium decreased by 10 to 40 msec in eight patients and increased by 20 and 30 msec in the remaining two patients

A V NODE *ERP* During the control period the ERP of the A V node could be determined in only 11 patients at one or more atrial cycle lengths In the remaining two patients atrial refractoriness exceeded that of the A V node and limited deter mination of the latter parameter ISOP de creased the ERP of the A V node in five of the 11 patients (Fig 3) by an average of 106 msec (range 20 to 190 msec) p value <0 01 In the remaining six patients ISOP decreased the A V nodal ERP to such a degree that the ERP of the atrium was encountered first The actual or lowest value for the ERP of the A V node could not be achieved and in these six patients is expressed as less than the ERP of the atrium (Table II)

FRP In all patients isoproterenol significantly decreased the FRP of the A V node (Fig 4) at all cycle lengths except one (Table II) The average decrease was 72 msec (range 10 200 msec) p value <0 001

HIS PURKINJE SYSTEM *RRP* In five patients (and 12 cycle lengths) the RRP of the HPS could be determined before and after isoproterenol A consistent shortening of the RRP of the HPS was seen after drug administration (Fig 5) The value for this parameter at 12 cycle lengths measured 433 7 msec S E M (standard error of the mean) 19 msec during the control period and 422 9 msec S E M 19 4 msec after ISOP (p value <0 001) In three patients (eight cycle lengths) the RRP of the HPS could only be demonstrated after the drug but not before These results are not unexpected if one considers that ISOP by decreasing the FRP of the A V node allows achievement of shorter H H_2 intervals

ERP The ERP of the HPS could not be determined in any patient in this study since complete block within the His Purkinje system did not occur either during the control or after drug infusion

Discussion

Administration of ISOP almost invariably results in simultaneous acceleration of the sinus node pacemaker and enhanced A V nodal con duction effects which were consistently observed in the present study Although not previously shown ISOP consistently decreased both the functional and effective refractory periods of the A V node

Kassebaum and Van Dyke demonstrated in isolated lamb Purkinje fibers that ISOP did not change conduction velocity Similarly Wallace and Sarnoff reported that sympathetic nerve stimulation in the intact dog heart produced little or no change of conduction velocity in the Purkinje system In a recent study using His bundle electrograms it was reported that ISOP consistently decreased HP conduction time (range 1 to 16 msec) in patients with either normal or prolonged HP conduction (H V inter vals)[8] We were unable to confirm these latter observations In the present study H V intervals remained unchanged after ISOP in the entire group which included four patients with pro longed H V intervals Several possible reasons can be put forth which may explain some of the discrepancies between the results of this study and those reported by Dhingra and associates[8]

(1) Part of the discrepancy may be related to the amount and rate of infusion of isoproterenol In the study by Dhingra and associates infusion was adjusted to achieve a sinus rate of between 100 to 120 per minute whereas in the present study measurements were obtained after several minutes of a constant infusion of 1 mcg per minute The average sinus rates after infusion were 104 beats per minute during the study by Dhingra and associates and 90 beats per minute during the present study It cannot be stated for certain whether isoproterenol in doses greater than those used in the present study will affect His Purkinje conduction time

(2) Changes in catheter position such that a proximal right bundle branch potential and not a bundle of His potential is recorded after isoprote renol infusion can result in an apparent shorten ing of the H V interval This possibility is sug gested by a change to a lower amplitude atrial electrogram when an RB potential is recorded as appears to be the case in panels A and B of Fig 1 of reference 8 In the present study an unchang ing catheter position is indicated by the constan cy of both the H V interval measurements and the amplitude of the atrial electrogram record ings

(3) Variations in paper speed can cause artifac tual changes in all interval measurements espe cially when time lines are inscribed every 1 000

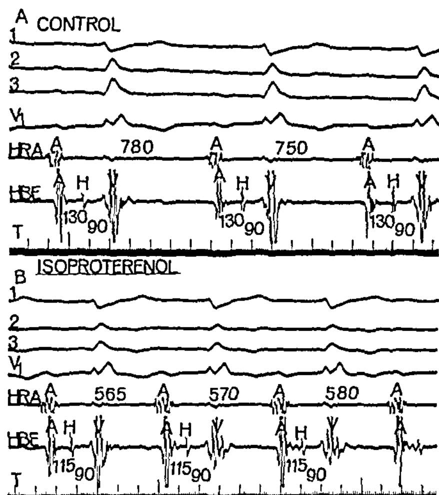


Fig 1 Effect of isoproterenol on sinus rate A V nodal and His Purkinje conduction Tracings in each panel from top to bottom are standard ECG Leads I II III V high right atrial electrogram (HRA) His bundle electrogram (HBE) and time lines at 10 and 100 msec Panel A shows sinus rhythm during the control period The sinus cycle length measures 780 to 750 msec The A H and H V intervals measure 130 and 90 msec respectively Note prolonged P R and aberrant QRS complex (right bundle branch block and left posterior hemiblock pattern) After isoproterenol (panel B) there is acceleration of the sinus rate a decrease in the A H interval (115 msec) and an unchanged H V interval (90 msec) and QRS complex

of conduction during rapid atrial pacing was significantly delayed after ISOP (Fig 2) Four of these 12 patients demonstrated 1 1 atrioventricular response up to paced atrial rates of 200 beats per minute following ISOP whereas in the control period the onset of A V nodal Wenckebach phenomenon occurred at average atrial rates of 165 beats per minute In the remaining eight patients A V nodal Wenckebach type of conduction occurred at an average atrial rate of 141 beats per minute (range, 130 to 170 per minute) during the control period and 175 beats per minute (range 160 to 190 per minute) after ISOP In the remaining two patients, a 1 1 atrioventricular response occurred up to maximum atrial paced rates of 200 beats per minute both before and after the drug administration

His-Purkinje system In all patients His Purkinje conduction time (H V interval) remained unchanged following ISOP, both during sinus rhythm (16 patients) and at various paced atrial rates (14 patients) The H V intervals during sinus rhythm were within normal range in 12 patients and prolonged in four patients (Table I Fig 1)

Antegrade refractory period studies 13 patients (Table II)

Atrium For the entire group of 13 patients including all cycle lengths the ERP of the atrium averaged 296 6 msec during the control and 323 msec after ISOP These differences did not achieve a statistical significance (p value >0 2) since both decrease and increase in atrial ERP was observed after ISOP As, for example when the atrial ERP was measured in 10 patients at a basic atrial cycle length of 600 msec the ERP of

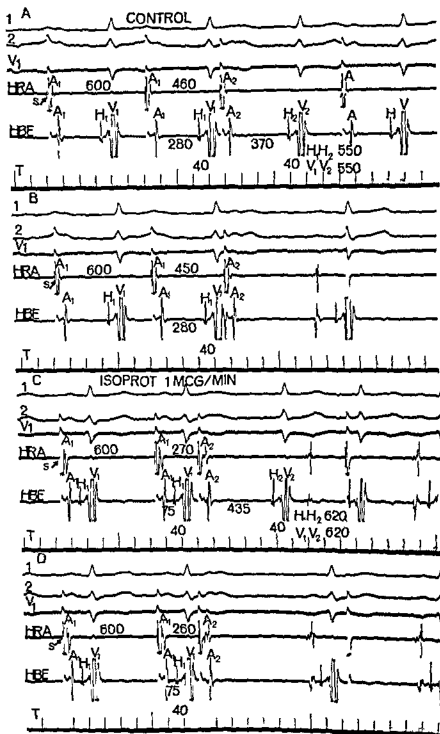


Fig 3 Effect of ISOP on the effective refractory period of the A V node At an atrial cycle length of 600 msec and an A A of 460 msec A conducts with an A H of 370 msec during the control (panel A) Upon decreasing the A A to 450 msec (panel B) A blocks proximal to the bundle of His which defines the effective refractory period of the A V node before ISOP Panel C demonstrates marked shortening of the A V nodal effective refractory period following ISOP such that A is still able to conduct at an A A interval of 2[illegible]0 msec Finally panel D demonstrates the effective refractory period of the A V node after ISOP which has decreased by 190 msec compared to the control period Note also marked shortening of A V nodal conduction time of the basic drive beats after ISOP (from [illegible]89 msec to 75 msec) and unchanged His Purkinje conduction time

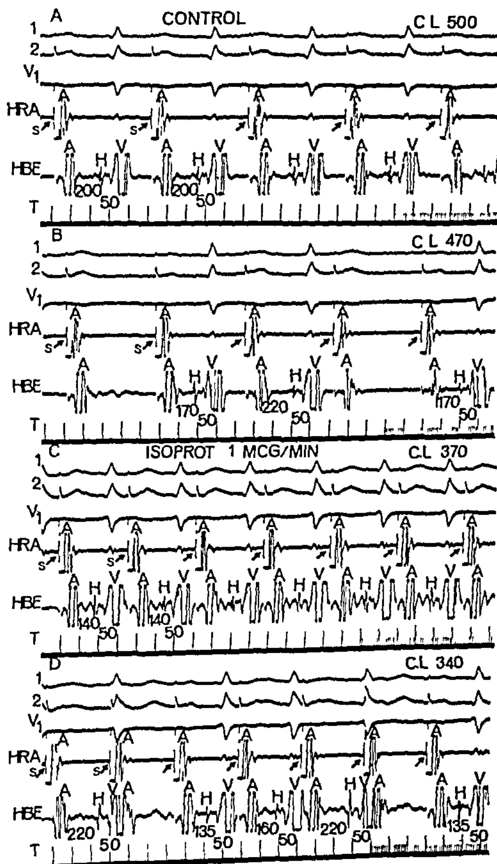


Fig 2 Effect of ISOP on A V nodal conduction Panel A demonstrates 1 1 atrioventricular response at a paced atrial cycle length of 500 msec during the control period The A H and H V intervals measure 200 and 50 msec respectively S denotes stimulus artifact Upon decreasing the atrial cycle length to 470 msec (panel B) a 3 2 A V nodal Wenckebach type of conduction results as indicated by progressive prolongation of the A H interval (from 170 to 220 msec) and block of the third atrial impulse in the A V node Panel C shows 1 1 A V conduction after ISOP at an atrial cycle length of 370 msec A 4 3 A V nodal Wenckebach is shown in panel D after ISOP Note the decrease in atrial cycle length necessary to produce A V nodal Wenckebach type of conduction following ISOP (from 470 to 340 msec) and also the unchanged H V intervals

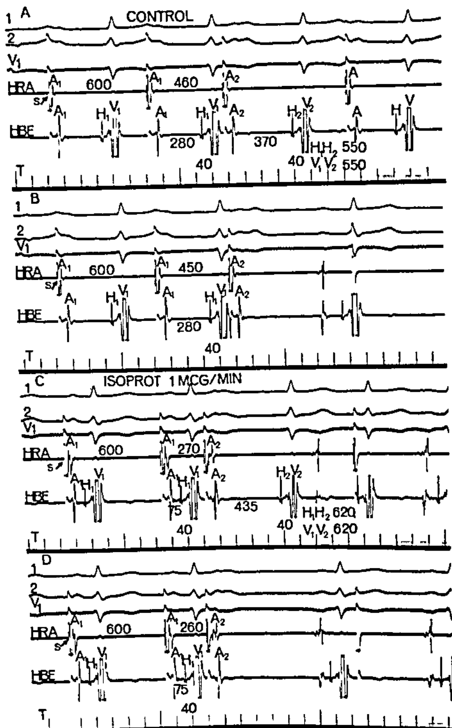


Fig 3 Effect of ISOP on the effective refractory period of the A V node At an atrial cycle length of 600 msec and an A A of 460 msec A conducts with an A H of 370 msec during the control (panel A) Upon decreasing the A A to 450 msec (panel B) A blocks proximal to the bundle of His which defines the effective refractory period of the A V node before ISOP Panel C demonstrates marked shortening of the A V nodal effective refractory period following ISOP such that A is still able to conduct at an A A interval of 270 msec Finally panel D demonstrates the effective refractory period of the A V node after ISOP which has decreased by 190 msec compared to the control period Note also marked shortening of A V nodal conduction time of the basic drive beats after ISOP (from 289 msec to 75 msec) and unchanged His Purkinje conduction time

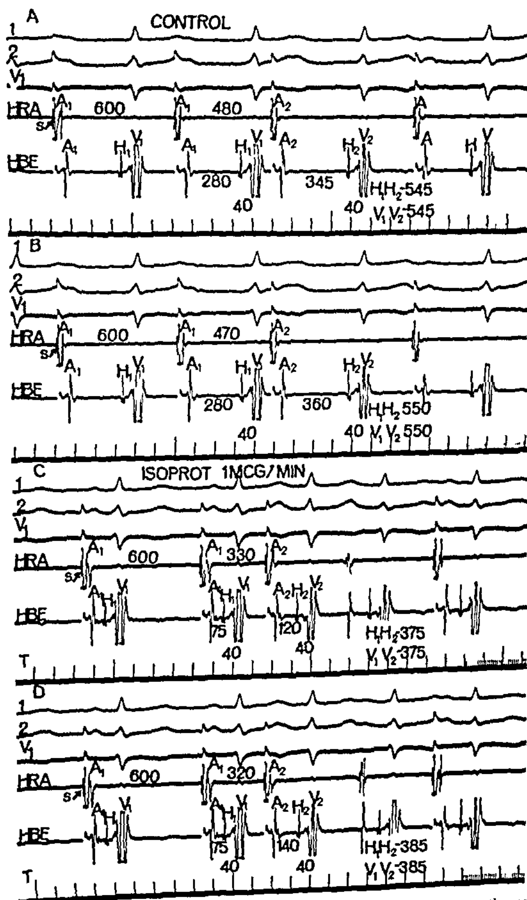


Fig 4 The effect of ISOP on the A V nodal functional refractory period Basic atrial cycle length is constant at 600 msec in all panels During the control period (panel A) at an atrial coupling interval of 480 msec A conducts within an A H of 345 msec The resulting H H interval of 545 msec defined the functional refractory period of the A V node in this patient at this cycle length Further decrease in A A interval (panel B) results in prolongation of H H interval of 550 msec Panel C demonstrates the functional refractory period of the A V node following ISOP (H H 375 msec) at an A A_1 of 330 msec

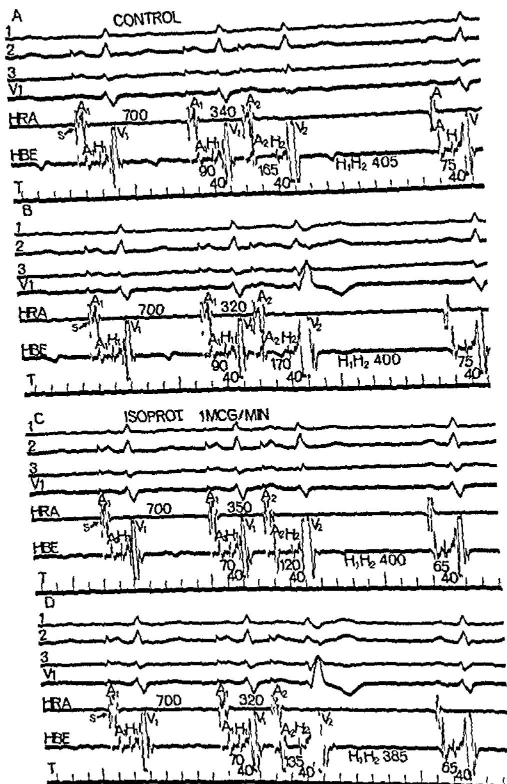


Fig 5 Effect of ISOP on the relative refractory period of the His Purkinje system Basic atrial drive is constant at 700 msec Before ISOP A results in minor aberration at an H H interval of 405 msec (panel A) and right bundle branch block pattern at an H H interval of 400 msec (panel B) Following ISOP similar degrees of ventricular aberrations could be produced at shorter H H intervals i.e 400 and 385 msec respectively (panels C and D)

msec[8] This problem can be minimized, although not completely eliminated, by recording (as was done in this study) continuous time lines at 10 and 100 msec intervals and using the time scale which is at the same perpendicular level as the interval to be measured

The magnitude of decrease in the RRP of the His Purkinje system (5 to 15 msec) following *isoproterenol represented a statistically signifi* cant 1 to 4 per cent change from control values The ERP of the HPS could not be reached in any of the patients in this study even though ISOP, by virtue of decreasing the functional refractory period of the A V node permitted the attainment of shorter H_1H_2 intervals than in the control

This in part resulted from the fact that ISOP significantly decreased the sinus cycle length in all patients which of itself produces a rate related decrease in the ERP of the HPS

Summary

The effects of isoproterenol (ISOP) on the functional properties of the A V conduction system were studied in 16 patients using His bundle recordings and the atrial extrastimulus technique In all patients ISOP at an infusion rate of 1 mcg per minute resulted in sinus acceleration and enhancement of A V nodal conduction but had no effect on His Purkinje conduction time ISOP significantly decreased both functional and effective refractory periods of the A-V node The relative refractory period of the His Purkinje system decreased by a small amount in five patients in whom the parameter could be compared before and after the drug

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Wolff-Parkinson-White syndrome
Mechanocardiographic study on the mechanical consequences of ventricular pre excitation

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In patients with the Wolff Parkinson White (WPW) syndrome a portion of ventricular myocardium is depolarized prematurely due to the existence of an anomalous atrioventricular pathway It would be extremely interesting to know what sort of mechanical prematurity is caused by this premature excitation However most previous studies on the WPW syndrome have been electrophysiologic and little is known of mechanical events in this syndrome

Previously we reported the results of analyses of the clinical history and symptoms electrocardiograms[3] and phonocardiograms[4] of patients with the WPW syndrome In this study the mechanical consequences of ventricular pre excitation were examined by comparing electrical and mechanical events in the ventricles during anomalous pathway conduction and normal atrioventricular conduction using a mechanocardiographic technique

Methods

Subjects

Patients with the WPW syndrome Studies were made on 20 patients aged 20 to 64 (average age 39) in whom anomalous pathway conduction was blocked by procaine amide resulting in normalization of conduction Of the 20 cases 11 were of type A (Group A) and 9 of type B (Group B) according to the classification of Rosenbaum and co workers[5] Cases of atypical forms such as those with variants of the classic WPW syndrome or with the Lown Ganong Levine syndrome[6,7] and cases in whom procaine amide was ineffective were excluded

Intravenous injection of a total of 500 to 1 200 mg (average 800 mg) of procaine amide at a rate of 100 mg per minute depressed the anomalous pathway Care was taken that the injection did not cause decrease in the systemic blood pressure Normalization of atrioventricular conduction was judged by disappearance of the delta wave prolongation of the P Q interval (to more than 0 12 second) and shortening of the QRS duration (to less than 0 10 second) and improvement in secondary S T T changes in the electrocardiogram

Control group Eight healthy persons aged 20 to 28 (average age 26) were employed as a control group (Group C) and the mechanocardiographic effects of procaine amide on them were observed The drug was injected intravenously in a total dose of 800 mg at a rate of 100 mg per minute

Technique for recording the mechanocardiogram The subjects were made to rest in the supine position for 30 minutes and then an initial mechanocardiogram was taken in the position of the left lateral decubitus After administration of procaine amide a second mechanocar

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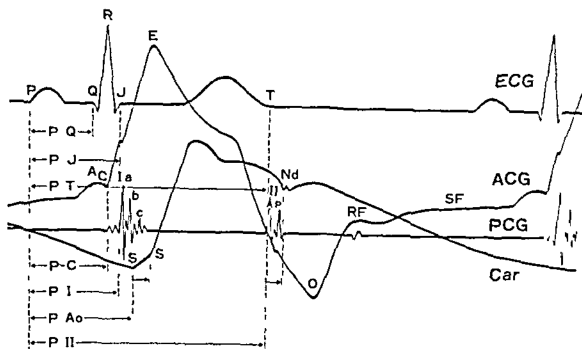


Fig 1 Schematic diagram indicating time intervals measured from the mechanocardiogram

diogram was recorded in the same posture Simultaneous recordings were made of the electrocardiogram (ECG), phonocardiogram (PCG) carotid arterial pulse wave (Car), and apexcardiogram (ACG) A multipurpose bioelectrograph (Fukuda Electro MR 400 series) was used with a paper speed of 100 mm per second and time lines of 10 milliseconds The ECG was taken in Lead II The PCG was picked up at medium frequency from Erb s area and the ACG was recorded at the point of maximal apical pulsation using a Fukuda Electro TY 302 when each pick up was kept in the examiner s hand For carotid arterial pulse tracing, the pick up (TY 302) was applied to the right common carotid artery and fixed by a supporting mechanism while the subject s head was turned to the left At the time of recording the subject stopped breathing half way through the expiratory phase Care was taken that this arrest of expiration did not become a Valsalva maneuver

Measurements from the mechanocardiogram The following time intervals were measured in milliseconds from the onset of electrical excitation of the atrium i e the starting point (P) of the P wave of the ECG (Fig 1)

P P Pulse interval

P Q Time from the onset of the P wave to the onset (Q) of the delta wave or QRS complex Point Q is the starting point of ventricular depolarization

P-J Time for the onset of the P wave to the end point (J) of ventricular depolarization

P T Time from the onset of the P wave to the end point (T) of ventricular repolarization

P C Time from the onset of the P wave to the onset (C) of the upstroke of the systolic wave Point C roughly corresponds to the starting point of the rise of intraventricular pressure [8]

P I Time from the onset of the P wave to the starting point (I) of the central phase of the first sound Usually point I corresponds to the time of closure of the mitral valve

P II Time from the onset of the P wave to the starting point (II) of the central phase of the sound Usually point II is the time of closure of the aortic valve

P Ao Time from the onset of the P wave to the time of opening (Ao) of the aortic valve This is obtained by subtracting the left ventricular ejection time (S to Nd of the carotid wave) from the P II interval

Abbreviations

State I This is the state before administration of procaine amide In Groups A and B it means the condition where pre excitation of the ventricle by anomalous pathway conduction occurs i e the pre excitation state The time intervals for example of P Q and P Ao in State I are expressed as $P\ Q_I$ and $P\ Ao_I$

State II This is the state after administration of procaine amide In Groups A and B it means

Table I Time intervals in State I (mean ± 1 S D in milliseconds) and significance of difference between these values in Groups A B and C

Time interval	Group			Significance of difference between		
	A	B	C	A and C	B and C	A and B
P P	864 ± 110	889 ± 132	891 ± 126	n	n	n
P Q	102 ± 11	90 ± 11	167 ± 24	ss	ss	s
P-J	225 ± 29	230 ± 14	240 ± 24	n	n	n
P T	527 ± 26	529 ± 47	540 ± 46	n	n	n
P C	174 ± 26	175 ± 14	193 ± ?3	n	n	n
P I	20? ± 21	205 ± 17	?19 ± 19	n	n	n
P Ao	243 ± 38	265 ± 27	275 ± 27	n	n	n
P II	516 ± 19	535 ± 38	548 ± 39	n	n	n

n not significant at P = 0 05 by the *t* test for unpaired variates
s significant at P < 0 05 ss significant at P < 0 01

Table II Time intervals in State II (mean ± 1 S D in milliseconds) and significance of difference between these values in Groups A B and C

Time interval	Group			Significance of difference between		
	A	B	C	A and C	B and C	A and B
P P	787 ± 133	806 ± 113	863 ± 94	n	n	n
P Q	171 ± 25	166 ± 23	174 ± 17	n	n	n
P J	261 ± 28	249 ± 26	247 ± 19	n	n	n
P T	587 ± 42	595 ± 50	548 ± 24	s	s	sn
P-C	202 ± 22	200 ± 23	200 ± 17	n	n	n
P I	233 ± 23	230 ± 20	221 ± 16	n	n	n
P Ao	287 ± 27	291 ± 37	282 ± 21	n	n	n
P II	549 ± 24	565 ± 37	557 ± ?6	n	n	n

n not signifi ant at P = 0 05 by th t t t fo u paired v riat
s signifi nt at P < 0 05 ss s gn fi ant at P < 0 01

the condition where the drug has inhibited ventricular pre-excitation i e the normalized state The intervals for example of P Q and P Ao in State II are expressed as PQ_{II} and PAo_{II}

Δ This shows the difference obtained by subtracting values in State II from those in State I for the same subject i e the extent of change in values due to procaine amide For example for the P Q interval $\Delta PQ = (PQ_I) - (PQ_{II})$

Statistical analysis of the measured values The values were examined statistically without correction for the heart rate First the mean and standard deviation (S D) of each time interval in each group were estimated as follows (1) the mean and 1 S D of the measured values in State I (2) the mean and 1 S D of the measured values in State II and (3) the mean of Δ i e the mean difference of values in State II from those in State I

The *t* test for a series of paired variates[9] was applied to estimate the significance of the mean of Δ values The *t* test for unpaired variates was used to examine the significance of the difference among three groups in (1) (2) or (3)

Results

Measured values in State I Table I shows the mean values of the time intervals of Groups A B and C in State I

PQ_I was significantly shorter in Groups A and B than in Group C (P < 0 01) Furthermore PQ_I was shorter in Group B than in Group A (significant at P < 0 05) The other time intervals were not significantly different in Groups A B and C

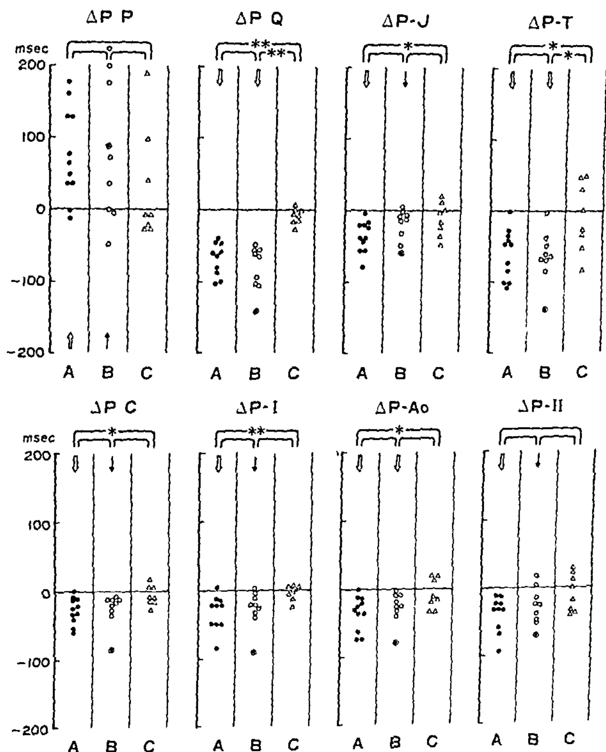


Fig 2 Difference between time intervals in States I and II in Groups A B and C Thick arrow significant at p < 0 01 by the t test for paired variates Thin arrow significant at p < 0 05 significant at P < 0 01 by the t test for unpaired variates significant at P < 0 05

but in general the intervals in Groups A and B tended to be shorter than those in Group C and the mean values of P Ao$_I$ and P II$_I$ in Group A in particular were more than 30 milliseconds shorter than those in Group C

Measured values in State II The only difference of the intervals in Groups A and B from those in Group C was that P T$_{II}$ was significantly longer (P < 0 05) Other intervals were similar (Table II) Moreover, the mean values of measurements of Groups A and B in State II were not significantly different from the mean values of Group C in State I

Comparison of measured values in States I and II Fig 2 shows the Δ values for each time interval in Groups A, B, and C, and their mean values are shown in Table III The Δ values of all time intervals except Δ P P in Groups A and B showed significant changes but in Group C, none of the Δ values showed a significant change

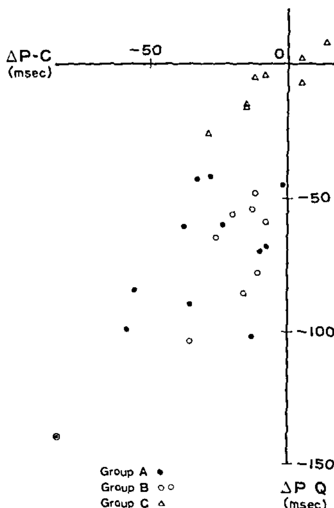


Fig 3 Relation between ΔP-Q and ΔP C

In Group A Δ P Q Δ P-J Δ P T Δ P C Δ P I and Δ P Ao were significantly larger than those in Group C while in Group B Δ P Q and Δ P T were significantly larger than those in Group C No significant differences were observed between any of the Δ values of Groups A and B

Fig 3 shows the relations between Δ P Q and Δ P C of all the individuals in the three groups In general Δ P Q was longer than Δ P C and this was more apparent in Group A than in Group B

However the case of type B shown by an open circle with a dot in Figs 2 and 3 was exceptional in that Δ P C Δ P I and Δ P Ao were larger than those of cases in Group A

Discussion

Effects of procaine amide on electrical and mechanical events in the heart Procaine amide like quinidine tends to reduce the excitability of cardiac muscle and the conductivity of the conduction system and has various actions on the sino atrial node [10] It has been reported that rapid intravenous injection of procaine amide causes hemodynamic changes such as decreases in cardiac output peripheral blood pressure and pulmonary arterial pressure However when infused slowly in small doses this drug does not impair circulatory function [10]

In this study the influence of 800 mg of procaine amide infused intravenously on the time intervals of mechanocardiograms was examined in healthy persons (Group C) Following the administration of procaine amide the mean value of P P tended to become shorter and the mean values of other time intervals to become longer but these changes were not statistically significant In Groups A and B none of the time

Table III Difference between time intervals in States I and II (mean ± 1 S D in milliseconds) and significance of difference in these values in Groups A, B, and C

Item	Group			Significance of difference between		
	A	B	C	A and C	B and C	A and B
ΔP P	77 ± 63	82 ± 98	28 ± 77	n	n	n
ΔP-Q	−68 ± 21†	−69 ± 18†	−8 ± 11	ss	ss	n
ΔP-J	−36 ± 21†	−14 ± 17	−7 ± 17	s	n	n
ΔP T	−60 ± 36†	−53 ± 21†	−8 ± 48	s	s	n
ΔP C	−28 ± 19†	−18 ± 9*	−7 ± 14	s	n	n
ΔP I	−31 ± 24†	−17 ± 13	−3 ± 11	ss	n	n
ΔP Ao	−35 ± 24†	−20 ± 13†	−7 ± 22	s	n	n
ΔP II	−34 ± 29†	−24 ± 22*	−10 ± 28	n	n	n

*significant at P < 0 05 by the *t* test for paired variates
† significant at P < 0 01
n not significant at P = 0 05 by the *t* test for unpaired variates s significant at P < 0 05 ss significant at P < 0 01

intervals after administration of procaine amide were significantly different from those in Group C before or after administration of the drug Therefore in the WPW syndrome the changes of the time intervals caused by procaine amide are not due to myocardial depression by the drug but mainly to the disappearance of atrioventricular conduction by the anomalous pathway

Influence of ventricular pre excitation on the mechanical consequences There is little information available on the relation between electrical and mechanical events in the ventricles in the WPW syndrome Bandiera and Antognetti[11] observed by roentgenkymography that early contraction occurs in a limited area of the base of the left ventricle in type A WPW and of the right ventricle in type B WPW Ferrer and co workers[12] measured the time interval between the beginning of the initial deflection of the QRS complex and the onset of right ventricular systole (Q RVs) and the time interval between the beginning of Q and the onset of a pressure rise in the brachial artery (Q BAs), and observed a delay in the onset of systole in both the right and left ventricles Samet, Mednick, and Schwedel[13] by electrokymographic studies, found evidence of delay in ejection from both ventricles in most cases regardless of the side of the anomalous pathway March, Selzer, and Hultgren[14] studied the mechanical consequences of anomalous atrioventricular excitation by means of phonocardiograms, carotid pulse tracings and data obtained by cardiac catheterization They reported a case of type B showing early beginning and termination of ejection from both ventricles and a case of type A showing premature completion of ejection from the left ventricle only and a case showing delay in mechanical contraction of both ventricles Aravanis and co workers[15] confirmed the presence of a precontracting area in the right ventricle from the results of right ventricular pressure tracings in type B WPW, but they observed no delay in the effective contraction of either ventricle from findings obtained by left and right heart catheterization

As reported previously[4] we also found that in the WPW syndrome during the pre excitation state, the first and second sounds appeared prematurely The premature beginning of the initial phase of the first sound, and the prolongation and increase in intensity of the first sound were more marked in Group A than in Group B

In this study, the mechanical consequences of ventricular pre excitation were investigated by mechanocardiography The findings obtained in this way are simply an indirect index of cardiac action and do not always agree completely with actual mechanical events in the heart These disadvantages of the method must be taken into account in evaluating the results obtained

Measurements were first taken in the resting state before administration of procaine amide (State I) Comparison of the mean values of measurements in State I in Groups A B and C showed that P Q_1 was much shorter in Groups A and B than in Group C and that P Q_1 was shorter

in Group B than in Group A The other intervals also tended to be shorter in Groups A and B and the mean values of P Ao_1 and P II_1 in Group A in particular were more than 30 milliseconds shorter than those in Group C In patients with the WPW syndrome all the time intervals except P P were significantly shorter in State I than in State II (after procaine) The difference between values in States I and II (Δ) was measured In Group A ΔP Q ΔP-J ΔP T ΔP C ΔP I and ΔP Ao were significantly larger than in Group C and in Group B ΔP Q and ΔP T were significantly larger than those in Group C

Thus in the WPW syndrome the P Q interval is greatly shortened Other time intervals are also shortened but less than P Q and P T Therefore it appears that in the ventricle the mechanical events such as the onset of ventricular contraction atrioventricular valve closure and the aortic valve opening and closure are accelerated by electrical pre excitation but the extent of acceleration of these events is less than the extent of the pre excitation Shortening of the P Q interval is greater in Group B than in Group A while prematurity of mechanical events tends to be more in Group A than in Group B

Interesting results were obtained on one case of type B These are shown by open circles with a dot in Figs 2 and 3 In type B WPW a portion of the right ventricle usually shows early excitation However in this case shortenings of the P C P I and P Ao intervals were greater than in any cases of type A WPW Recently Lister and co workers[16] also reported a case of type B WPW in which an anomalous pathway entered the posterior base of the left ventricle near the crux of the heart They pointed out that analysis of ECG s is not a completely satisfactory method for locating an abnormal atrioventricular connection Such discrepancies between electrical activation and mechanical consequences may be due to the location of the anomalous pathway or to the presence of a number of pathways[1 5]

Summary

To elucidate the mechanical consequences of ventricular pre-excitation in patients with the WPW syndrome electrical and mechanical events in the ventricles during anomalous pathway conduction and normal atrioventricular conduction were examined mechanocardiographically in 11 cases of Group A and 9 cases of Group B in whom anomalous pathway conduction was stopped by procaine amide resulting in normalization of conduction Eight healthy persons were employed as a control group

In the control group procaine amide had no significant effect on the mechanocardiographic values In the WPW syndrome significant prolongation of the P Q P-J P T, P C P I P Ao and P II intervals was induced by the drug From the results of statistical analyses of measured values it would appear that mechanical events in the ventricles were accelerated by ventricular pre excitation but the extent of acceleration of the former was less than the extent of prematurity of the latter The anomalous ventricular pre excitation occurred earlier in cases of Group B than in those of Group A while initiation of ventricular contraction atrioventricular valve closure and aortic valve opening were accelerated more in Group A In one case of Group B electrical phenomena could not be related to mechanical events

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Hemodynamic effects of slow and rapid defibrination with defibrizyme, the thrombin like enzyme from venom of the timber rattlesnake

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The hematocrit and plasma viscosity are important determinants of the rate of oxygen transport in the mammalian circulation [*] The plasma viscosity has been shown to be a sensitive indicator of changes in fibrinogen and total globulin concentration [11] The hyperfibrinogenemic state which often develops subsequent to acute myocardial infarction should therefore increase plasma viscosity and decrease myocardial oxygen delivery In addition the hematocrit tends to be elevated after acute myocardial infarction[12, 3] and thus may contribute to increased blood viscosity with a concomitant reduction in oxygen delivery to the myocardium Gordon and coworkers have recently presented a theoretical model of the myocardial circulation which indicates that hyperfibrinogenemia and increased plasma viscosity may play a detrimental role after myocardial infarction

It would appear then that defibrination may have valuable clinical application in the immediate postinfarction period especially in view of the work of Maroko and associates[15, 16] on coronary artery reperfusion which suggests that up to at least 3 hours after myocardial infarction resumption of flow is capable of minimizing quite dramatically the size of the infarct

Although recent work by Ehrly[17] has described the influence of Arvin the thrombin like enzyme from venom of the Malayan pit viper on the flow properties of human blood little is known about the effects of either slow or rapid defibrination on the cardiovascular system The present study was undertaken to investigate the hemodynamic responses to defibrination in the dog and constitutes a portion of a much larger investigation[18, 19] designed to establish the potential use of defibrizyme the thrombin like enzyme from the venom of the timber rattlesnake (*Crotalus h horridus*) for therapeutic defibrination

Materials

The defibrinating enzyme from *Crotalus h horridus* venom was prepared in homogeneous form by procedures previously described [8, 9] In vitro a 1 0 mg per milliliter solution clotted control plasma or human fibrinogen in the absence of thromboplastin at a similar rate as 10 NIH units of thrombin (Parke Davis) Fibrinogen degradation product determination kits were obtained from Burroughs Wellcome Laboratories

Methods

The following coagulation procedures were used fibrinogen by the method of Ratnoff and Menzie[20] fibrinogen fibrin degradation products (FDP) by latex agglutination technique[?] one stage prothrombin times by the method of Quick[22] using an automatic clot timer (Fibrometer Bioquest Laboratories Maryland)

Experiments were performed on adult dogs of both sexes, from our beagle colony Prior to use each dog received a standard but thorough

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physical check up, including heart rate, rectal temperature, respiratory rate, electrocardiogram, and auscultatory examination for the presence of basilar râles and other indications of pulmonary congestive disease Thirty animals which were judged to be normal and within the weight range of 9 to 14 kilograms were chosen for this study They were fed standard canine ration (Purina) and water ad libitum However, food was with held for 12 hours prior to the experiment

Dose response The dose response to the defi brinating enzyme (henceforth called *defibrizyme*) was tested under the following experimental protocol Group I (10 dogs) received 0 83 mg of defibrizyme per kilogram of body weight Group II (5 dogs) received 0 50 mg of defibrizyme per kilogram of body weight Group III (5 dogs) re ceived 0 20 mg of defibrizyme per kilogram of body weight All doses were dissolved in 2 c c of sterile, physiologic saline and administered by the intravenous route through the femoral vein Two blood samples (controls) were collected prior to induction of defibrination and at 30 minutes 1, 2 3, 4, 5, 8, 12, and 24 hours after defibrination and analyzed for prothrombin times FDP and plasma fibrinogen Each time that a sample of blood was collected, it was replaced with an identical volume of sterile saline in order to avoid drastic changes in the total blood volume

Hemodynamic evaluation Ten animals were used to investigate the hemodynamic effects of slow (5 dogs) and rapid (5 dogs) defibrination Each dog was anesthetized with intravenous in jection of sodium pentobarbital (30 mg per kilo gram of body weight) and intubated, and respira tion was maintained with a Bennet respirator (Model RR 1) with the use of a standardized gas mixture of 20 per cent oxygen and 80 per cent nitrogen Cut down procedures were performed under sterile conditions

All dogs underwent the standard right and left heart catheterization procedure used in this labo ratory Right heart pressures were obtained through a polyethylene catheter (Intramedic PE160) and pulmonary artery and pulmonary capillary wedge pressures by means of a flow directed catheter (Swan Ganz Edwards Labora tories) advanced via the left jugular vein

An Intramedic PE205 polyethylene catheter was positioned in the left ventricle by way of the left femoral artery For determinations of cardiac output (dye dilution), a catheter (PE205) was positioned in the right ventricle via the left jugular vein Arterial blood was withdrawn through a catheter (PE205) inserted into the left carotid artery with a Harvard infusion with drawal pump using a 20 c c glass syringe at a rate of 19 4 c c per minute Aortic pressure (abdomi nal) was determined through a polyethylene catheter inserted into the aorta via the right femoral artery Pressures were measured with Statham transducers for venous (23BB), arterial (P23Db), and left ventricular (P23Gb) pressures

Left ventricular end diastolic pressures were measured at a high level of sensitivity (1 mm Hg equal to 4 mm paper) Arterial blood gases and pH were determined with an Instrumentation Laboratories (Model 113) gas analyzer Pressures were continuously recorded on a Honeywell multichannel photographic recorder (Visicorder Model 1508), with the exception of central venous pressure which was read directly from a water manometer Zero reference pressure was at the mid chest level The cardiac output curves were inscribed in the recorder for calculation by means of the Williams[23] formula From the hemody namic data in each dog additional parameters were calculated as follows

a *Systemic resistance* From the formula Ao × 100 CI where Ao is the mean aortic pressure and CI is the cardiac index in milliliters per kilogram per minute

b *Left ventricular minute work index (MWI) in G M/Kg per minute from the formula* MWI = CI × Ao × 1 36/100, where 1 36 is the mercury correction factor

c *Pulmonary vascular resistance by the formula* $\overline{PA}$ – WP × 1,332/C O where $\overline{PA}$ is the mean pulmonary artery pressure, WP is the capillary wedge pressure and C O is the cardiac output in milliliters per second, 1 332 is the conversion factor for dynes cm sec $^{-5}$

Rapid (bolus) defibrination was accomplished by administering the defibrinating enzyme intra venously at a dose of 1 0 mg per kilogram of body weight dissolved in 2 c c of physiologic saline solution through the femoral vein Slow defibri nation was undertaken in a similar manner but the enzyme was administered by infusion in 100 c c of saline solution over a period of 60 minutes

In these experiments each dog served as its own

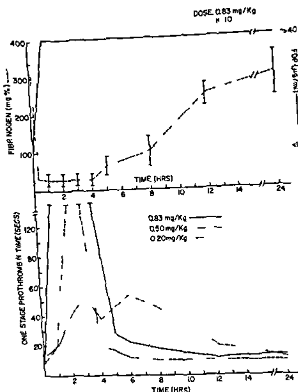


Fig 1 *Upper* Fibrinogen and fibrinogen degradation products (*FDP*) in 10 dogs receiving 0.83 mg of defibrizyme per kilogram of body weight. Each point represents the mean ± standard error of the mean. *Lower* Prothrombin times in dogs receiving 0.83 mg /Kg (n = 10) 0.50 mg /Kg (n = 5) and 0.20 mg /Kg (n = 5) of defibrinating enzyme

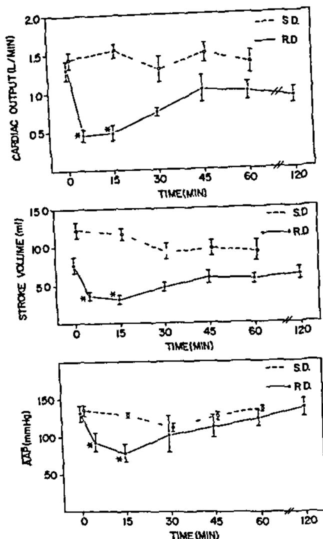


Fig 2 Cardiac output, stroke volume and mean systemic arterial pressures in dogs undergoing slow defibrination (*S D* n = 5) and rapid defibrination (*R D* n = 5). The dose in all cases was 0.83 mg /Kg of body weight. Each point represents the mean ± standard error of the mean. The asterisks denote those points which are statistically significantly different from control ($p < 0.01$)

control. All data were analyzed by calculating means, standard deviations of means and probability values using standard statistical methods.

Results

Dose response Rapid (bolus) intravenous administration of defibrizyme at dose levels of 0.83 and 0.50 mg per kilogram of body weight produced an anticoagulant state (within 30 minutes) characterized by infinite prothrombin times and plasma fibrinogen levels below 30 mg per 100 ml of blood.

As shown in Fig 1 clotting times returned to normal levels within 6 to 8 hours when the intermediate dose (0.50 mg /Kg) was used to achieve defibrination, wheras at a dose of 0.83 mg /Kg anticoagulation was achieved from 12 to 14 hours. The plasma fibrinogen concentration (see Fig 1) for 10 dogs receiving 0.83 mg /Kg dropped to 30 mg per cent and remained at this level for 4 hours, after which time a slow but continuous rise was observed until normal levels were again reached at approximately 24 hours.

The lower dose of 0.20 mg /Kg led to prothrombin times 4 to 5 times higher than control for periods of up to 8 hours. Concomitant with the drop in plasma fibrinogen levels there was as expected a drastic increase in serum FDP. These elevated FDP concentrations remained at over 40 µg per milliliter for 24 hours or longer in spite of steadily rising plasma fibrinogen concentrations.

Rapid defibrination did not induce visible side

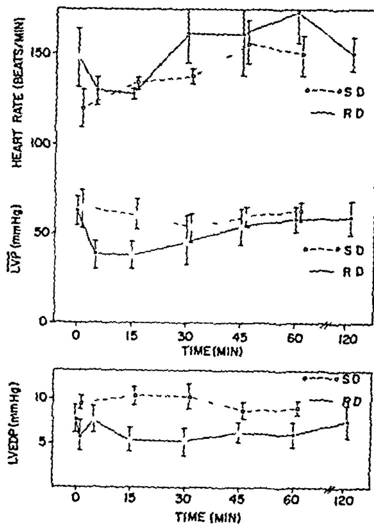


Fig 3 Changes in heart rate mean left ventricular (LVP) and left ventricular end diastolic (LVEDP) pressures induced by slow and rapid defibrination Other symbols as in Fig 2

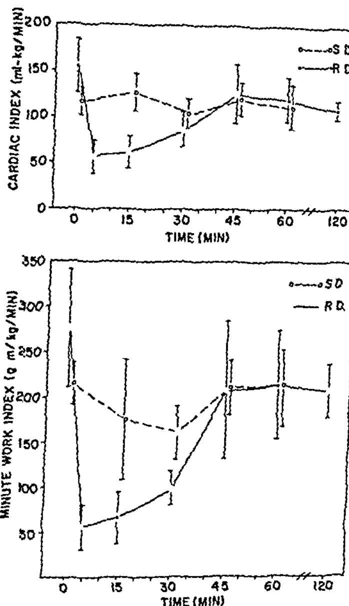


Fig 4 Changes in cardiac and minute work indices induced by slow and rapid defibrination in dogs

effects at the two lower doses (0 20 and 0 50 mg / Kg) however the group of dogs (10) undergoing rapid defibrination at the highest dose (0 83 mg / Kg) exhibited the following side effects vomiting (4/10) defecation (5/10) and skeletal muscle weakness (10/10) characterized by an inability to stand (6/10) or walk (8/10) In addition bradycardia (10/10) and a shift to heavy abdominal breathing (10/10) were common findings All of these effects subsided within 15 to 30 minutes after bolus administration of the defibrinating enzyme at the highest dose

Hemodynamic evaluation The hemodynamic effects of slow and rapid defibrination induced by the administration of 0 83 mg /Kg of defibrizyme were studied in 10 animals after a complete cardiac catheterization

As shown in Fig 2 there was a significant ($P < 0.01$) drop in cardiac output, stroke volume and mean aortic arterial pressure immediately after rapid induction of defibrination There was a decrease in heart rate and mean left ventricular pressure but the left ventricular end diastolic pressure was essentially unchanged (Fig 3) Cardiac and minute work indices dropped (Fig 4) and pulmonary artery pressure increased (Fig 5) Pulmonary capillary wedge, mean right ventricular and central venous pressures were not altered by rapid defibrination (see Fig 5) The calculated values obtained for systemic and pulmonary vascular resistances are depicted in Fig 6 Both parameters were drastically increased as a result of rapid defibrination whereas arterial Po Pco and pH were not affected (Fig 7)

Induction of defibrination by slow intravenous infusion did not cause significant hemodynamic alterations These results are shown for each parameter in comparison to the effects observed with rapid defibrination in Figs 2 to 6

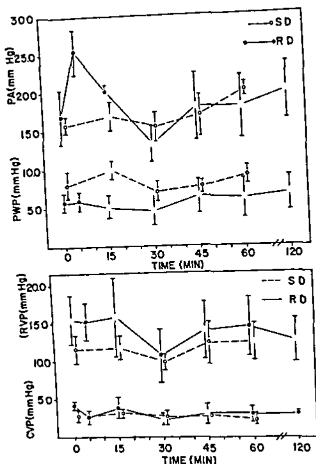


Fig 5 Mean pulmonary artery (*PA*) pulmonary capillary wedge (*PWP*) mean right ventricular (*RVP*) and central venous (*CVP*) pressure alterations induced by slow (*S D*) and rapid (*R D*) defibrination

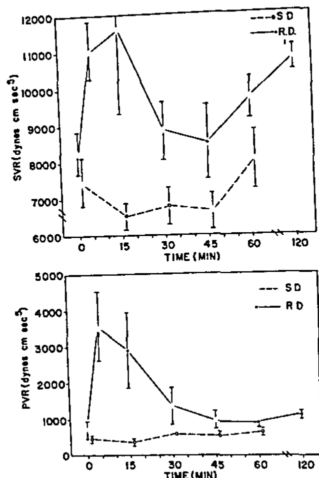


Fig 6 Changes in calculated systemic vascular (*SVR*) and pulmonary vascular (*PVR*) resistances after defibrination in dogs *S D* Slow defibrination *R D* Rapid defibrination In each case n = 5

Discussion

In recent years there has been an increasing interest in a new approach to anticoagulation by therapeutic defibrination To this effect defibrinating enzymes from the venom of the Malayan pit viper (*Agkistrodon rhodostoma*)[24, 2] commercially known as Ancrod and that of the neotropical viper *fer de lance* (*Bothrops atrox*)[8] commercially known as Defibrase[†] have been used

The present study reports the results of a pilot investigation designed to elucidate the hemodynamic effects of slow and rapid defibrination in the dog Because of the small number of dogs used in this preliminary study a high level of significance ($P < 0.01$) was sought in the statistical analysis of the data

After rapid defibrination a statistically significant decrease in cardiac output stroke volume and mean aortic arterial pressure was observed A drastic decrease although not significant for this small number of animals was also apparent in heart rate mean left ventricular pressure and cardiac and minute work indices Drastic but nonsignificant increases in both pulmonary and systemic vascular resistances and pulmonary artery pressures were also induced by rapid defibrination In contrast to these results slow defibrination caused little or no apparent change in the hemodynamic profile of the 5 dogs investigated These findings are in agreement with previously published reports from our laboratory on the efficacy and safety of slow defibrina

Ancrod, previously known as Arvin is a product f Twyf rd Laboratories, Lond n, N.W. 10 Engla d

†Defibrase is p od t f P tapharm Ltd B le Swit land

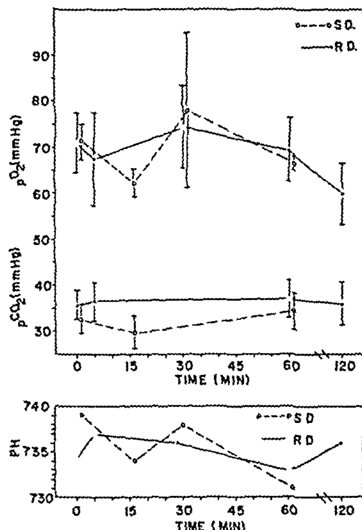


Fig 7 Arterial P_{O_2}, P_{CO_2} and pH in dogs undergoing slow and rapid defibrination Other symbols as in Fig 2

tion by the intravenous route with defibrizyme and with the work of Klein and co workers[30] on the effect of slow defibrination with Arvin upon cardiac function

An increasing amount of work continues to be reported relative to therapeutic defibrination for the treatment of deep vein thrombosis postoperative thrombotic complications pulmonary embolism, priapism and other complications related to abnormal rates of fibrinogen fibrin conversion and fibrin polymerization An extensive review on the subject has been published recently [31]

To our knowledge, however, the potential hazards of a rapid decrease in the viscosity of the blood brought about by the rapid decline in plasma fibrinogen concentrations have not been investigated Recent reports by Maroko and co workers[15 16] on coronary artery reperfusion and the theoretical approach undertaken by Gordon and associates [14] which indicate that a decrease in plasma viscosity may have potential use in the treatment of myocardial infarction, led us to undertake the present investigation into the hemodynamic effects of *rapid defibrination* Whereas slow defibrination appears to be a passive procedure rapid defibrination is not without consequences as shown by its effects on the cardiac output, stroke volume, arterial pressure, and other dependent variables

These results warrant further investigation into the mechanisms involved in the hemodynamic derangements observed with rapid defibrination Detailed studies into the effects of rapid defibrination on myocardial contractility, with the use of a larger number of animals, are now under way in our laboratory Above all, a highly significant two part question arises from this investigation (1) Does a very rapid decline in plasma fibrinogen concentration and/or blood viscosity induce a myocardial ischemic like defect? (2) If so, does this have any correlation with acute myocardial infarction and the sudden death syndrome? Answers to these questions must await the results of ongoing investigations.

Summary

The hemodynamic response to slow and rapid defibrination was studied in anesthetized beagle dogs with the following results

1 Slow defibrination was a benign procedure that had little or no effect on the hemodynamic variables studied

2 Rapid defibrination induced statistically significant decreases in cardiac output, stroke volume, and mean aortic arterial pressure

3 Bradycardia a drop in mean left ventricular pressure, cardiac and minute work indices, an increase in pulmonary artery pressure, and a drastic rise in pulmonary and systemic vascular resistances were also observed Although physiologically apparent, these changes were not statistically significantly different from control levels

4 Pulmonary capillary wedge pressure left ventricular end diastolic pressure arterial pH and blood gases were not altered by rapid defibrination

5 In view of the similarities between the hemodynamic changes observed after rapid defibrination and acute myocardial ischemia the role of decreasing fibrinogen concentrations and blood viscosity in acute myocardial infarction and the sudden death syndrome is questioned

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Effects of dexamethasone on myocardial cells in the early phase of acute myocardial infarction

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Libby and co workers[1] have shown that pharmacologic doses of cortisol limit infarct size 24 hours after coronary artery occlusion in dogs Although the mechanism of the beneficial action of glucocorticoids upon the myocardium is unclear several mechanisms could play a role in their protective effect on the myocardium These mechanisms are coronary vasodilation, improved myocardial contractility and stabilization of cellular membranes within the ischemic myocardium The membrane stabilizing action of the drug would be reflected by a diminished loss of myocardial cellular enzymes from the ischemic portion of the myocardium Since lysosomal hydrolases have been implicated in the propagation of the cellular injury during the early stages of acute myocardial infarction,[2] this action may be crucial in protecting the heart against ischemic damage Moreover, glucocorticoids are very effective in stabilizing lysosomal membranes Recently we demonstrated such an effect for the glucocorticoid, methylprednisolone[3] Since methylprednisolone and dexamethasone have been shown to have similar beneficial effects in other conditions of circulatory dysfunction,[4, 5] the present study was undertaken to investigate whether pre or posttreatment with dexamethasone alters myocardial enzyme release or electrocardiographic signs of myocardial damage during acute myocardial ischemia

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Method

Coronary artery occlusion Twenty one male and female cats (2 3 to 3 6 kilograms) were anesthetized with sodium pentobarbital (30 mg per kilogram) given intravenously The trachea was cannulated and positive pressure respiration was instituted with a Harvard respirator Catheters were placed within the right external jugular vein and left common carotid artery and positioned for the recording of central venous pressure (CVP) and mean arterial blood pressure (MABP), respectively Intravascular pressures were recorded continuously using appropriate Statham P 23 pressure transducers coupled to a Beckman Type R Dynograph Needle electrodes were placed subcutaneously to allow continuous recording of Lead III of the electrocardiogram (ECG) A mid sternal thoracotomy was performed, the heart exposed, and a noncannulating electromagnetic flow probe placed around the root of the aorta The output of the flow probe was amplified by a Statham Model 4001 flowmeter and continuously recorded on the oscillographic recorder The left coronary artery was cleared of surrounding tissue and a 3-0 silk ligature was placed under the vessel In cats subjected to acute myocardial ischemia, the ligature was tied tightly around the left coronary artery 13 to 15 mm from the coronary ostium Cats were either sham operated or subjected to five hours of myocardial ischemia (MI) following occlusion of the coronary artery Cats subjected to MI were given either dexamethasone sodium phosphate (Decadron Merck) 8 mg per kilogram or an equal volume of vehicle in

the jugular vein catheter Dexamethasone was administered slowly over ten minutes beginning either 30 minutes prior to or 60 minutes following occlusion of the coronary artery Sham operated cats were given dexamethasone 30 minutes prior to the start of the experiment

Sampling and homogenization of cardiac tissue Samples of arterial blood (4 ml) were withdrawn from the carotid catheter just prior to occlusion and at one two four, and five hours after occlusion Blood samples were drawn from sham operated cats at the same time Blood loss was replaced with an equal volume of Krebs Henseleit solution warmed to 37° C Blood was collected in polyethylene tubes containing two drops of sodium heparin 1 000 units per milliliter (Upjohn beef lung) and centrifuged at 2 400 × g and 4° C for 15 minutes The plasma was decanted and treated as described below At five hours the hearts were excised rinsed in 0 9 per cent NaCl solution at 4° C rapidly weighed and placed in cold 0 25 M sucrose The heart was divided into ischemic and normal left ventricle by inspection of the coronary vessels endocardium and epicardium Thus tissue supplied by arterial branches distal to the ligature appeared as a cyanotic area having patchy subendocardial hemorrhagic regions

Ischemic or nonischemic tissue was homogenized in 0 25 M sucrose (1 10 w v) containing 1 mM ethylenediaminetetraacetic acid and 0 1 mM mercaptoethanol for the determination of myocardial creatine phosphokinase (CPK) activity[6] The tissue preparations for the CPK determinations were treated according to the method of Kjekshus and Sobel Additional ischemic or adjacent normal ventricular tissue was minced and homogenized in 0 25 M sucrose (1 10 w v) for subsequent determination of lysosomal enzymes Each sample of myocardium was homogenized twice for 15 seconds using a Virtis homogenizer at a speed setting of 9 0 The homogenates were centrifuged at 800 × g for 10 minutes The supernatants were centrifuged at 36 000 × g for 30 minutes at 4° C Supernatants were assayed for β glucuronidase and cathepsin D activities in the presence and absence of Triton X 100 Cardiac homogenates from sham operated cats were derived from left ventricular tissue anatomically equivalent to the ischemic and normal areas present in ischemic hearts

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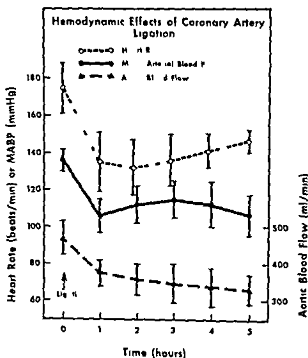


Fig 1 Hemodynamic effects of coronary artery ligation in cats receiving the vehicle for dexamethasone 30 minutes prior to ligation Ligation of the left coronary artery 13 to 15 mm from the coronary ostium produced significant decreases in the heart rate mean arterial blood pressure and aortic blood flow Values are means ± S E M for four cats

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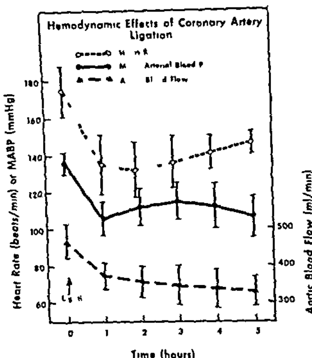


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Fig 1 illustrates the heart rate mean arterial blood pressure and aortic blood flow just prior to and for five hours following coronary ligation in untreated cats (i e cats receiving the vehicle for dexamethasone) Ligation of the coronary artery

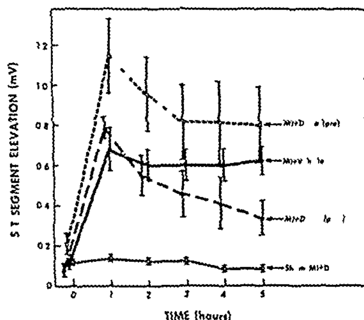


Fig 2 Effect of dexamethasone (Dexa) or its vehicle upon the elevation of the S T segment in cats subjected to acute myocardial ischemia (MI) by occlusion of the left coronary artery All values are means ± S E M for four to six cats in each group Sham operated cats given Dexa showed an absence of S T segment elevation over the entire five hour experimental period Occlusion of the left coronary artery initially produced similar elevations of the S T segment in all three groups of occluded cats The S T segment of vehicle treated cats (MI + vehicle) remained elevated for the duration of the experiment However S T segment elevation declined toward control values five hours after occlusion in MI cats posttreated with Dexa (MI + Dexa post) mV = millivolts

produced moderate but statistically significant ($p < 0.02$) decreases in heart rate, mean arterial blood pressure and aortic flow within one hour Furthermore, the hemodynamic response of ligated cats receiving dexamethasone did not differ from that of the animals given vehicle In contrast to cats experiencing coronary artery ligation, sham operated cats maintained stable normal values for heart rate, blood pressure and aortic flow over the five hour experimental period Furthermore, the directly measured central venous pressures and the calculated total peripheral resistances of untreated cats were similar to dexamethasone treated cats throughout the postocclusion period Thus we do not find any overt hemodynamic action of dexamethasone in our experiments with regard to systemic vasodilator or positive inotropic effects

In four cats, ventricular fibrillation occurred spontaneously 20 to 30 minutes after coronary artery ligation Cats experiencing a single episode of ventricular fibrillation were rapidly converted to sinus rhythm using a Medtronic Internal External defibrillator (Minneapolis Minn) For the remainder of the experimental period, these cats displayed mean hemodynamic parameters and loss of myocardial enzymes which were similar to the majority of cats without ventricular fibrillation Cats in which the ventricle fibrillated a second time were discarded

The S T segment elevation recorded in dexamethasone treated and untreated cats is shown in Fig 2 Sham operated cats given dexamethasone exhibited no significant change in S T segment elevation during five hours of observation In contrast, marked elevation of the S T segment occurred at 20 to 60 minutes in all groups of cats subjected to coronary artery occlusion Moreover, S T segment remained elevated for the entire experimental period in untreated cats and in cats pretreated with dexamethasone However, post treatment of ischemic cats with dexamethasone was associated with a significant reduction in the S T segment five hours after coronary artery occlusion

Concomitant with the observed electrocardiographic changes increases in plasma CPK activities occurred in all experimental groups (Fig 3) A significant elevation of plasma CPK activity occurred as early as two hours following coronary artery occlusion in untreated cats Plasma CPK activity continued to increase, reaching a value of eight times the initial plasma CPK activity five hours after coronary artery occlusion In contrast, sham operated cats exhibited only a moderate increase in plasma CPK activity after five hours Moreover both pre and posttreatment of cats with dexamethasone limited the increase in plasma CPK activity so that five hours after coronary artery occlusion plasma CPK activity was not significantly different from sham operated control animals

Although plasma CPK activities were altered by MI, the plasma activities of β glucuronidase and cathepsin D remained unchanged for the five hour experimental period The absence of increased plasma lysosomal hydrolase activities following myocardial ischemia correlated well with the relatively well maintained mean arterial blood pressure and aortic flow in coronary ligated cats (Fig 1) Adequate tissue perfusion in peripheral organs prevented loss of lysosomal hydrolases from noncardiac tissues

In contrast to the plasma activities of the lysosomal hydrolases β glucuronidase and ca

thepsin D the myocardial activities of these enzymes were affected by coronary artery liga tion Fig 4 summarizes the myocardial cathepsin D activities of normal and ischemic myocardial tissue obtained from dexamethasone treated and untreated cats In cats subjected to sham MI (i e coronary artery isolated but not ligated) normal tissue and tissue which would have become ischemic if the coronary artery had been ligated had very similar activities of the lysosomal protease cathepsin D (i e about 20 units per milligram of protein) Futhermore nonischemic myocardial tissue of hearts subjected to coronary ligation also showed a cathepsin D activity approximating 20 units per milligram of protein However ischemic myocardial tissue of cats given the steroid vehicle exhibited a 40 per cent reduc tion in cathepsin D activity compared to the activity of adjacent normal tissue or to left ventricular tissue excised from sham operated cats In contrast ischemic myocardial tissue of cats given dexamethasone one hour after corona ry artery ligation exhibited a cathepsin D activity similar to that of normal tissue 23 9 ± 2 1 units vs 20 7 ± 1 4 units respectively However pretreatment with dexamethasone appeared less effective in preventing the loss of myocardial cathepsin D Thus ischemic tissue of pretreated cats had 16 per cent less protease activity when compared to adjacent normal tissue ($p < 0.02$)

The alterations in myocardial CPK activities (Fig 5) were very similar to those of cardiac cathepsin D and reflected the changes found in plasma CPK activities in the four experimental groups Thus the CPK activity of ischemic tissue of untreated MI cats was 40 per cent lower than the normal ventricular tissue of these hearts Furthermore posttreatment of MI cats with dexamethasone significantly prevented the loss of enzyme activity from the ischemic myocardium However pretreatment with dexamethasone was significantly less effective than posttreatment in preventing loss of CPK activity from the ischemic portion of the myocardium Ischemic tissue of pretreated cats had 30 per cent less enzyme activity than adjacent normal tissue a level of enzyme activity not significantly different from that observed in ischemic tissue of untreated cats

Assay of the cardiac activities of the lysosomal hydrolase β glucuronidase in normal and is chemic myocardium presented a similar pattern

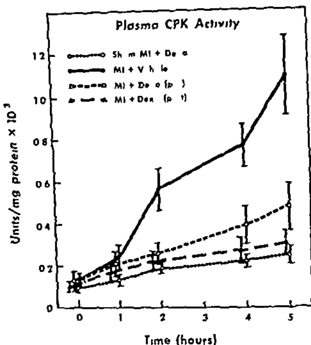


Fig 3 Effect of dexamethasone or its vehicle upon plasma CPK activity before and after induction of acute myocardial ischemia (MI) All values are means ± S E M expressed in International Units (IU) × 10⁻ per milligram of protein Plasma CPK activity increased eightfold in cats given vehicle prior to occlusion A significant increase in plasma CPK occurred as early as two hours after occlusion Treatment of cats with dexamethasone 30 minutes before or 60 minutes after occlusion prevented much of the increase in plasma CPK activity following MI

to that observed for cardiac cathepsin D and CPK activities

Discussion

Ligation of the coronary artery produced moderate decreases in heart rate mean arterial blood pressure and aortic flow (Fig 1) However pharmacologic doses of dexamethasone given either before or after coronary artery ligation did not alter this hemodynamic pattern from that of cats given only the vehicle for dexamethasone (i e sterile water containing the steroid preserva tives) These data indicate that dexamethasone does not alter the hemodynamic response to ischemia at least within the first five hours following coronary artery occlusion Thus we do not find any overt vasodilating or positive inotropic effect of dexamethasone in these experi ments This lack of a hemodynamic effect is in agreement with earlier findings[4] in dogs and in cats[2] wherein pharmacologic doses of dexameth

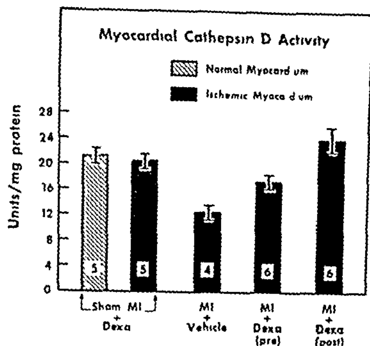


Fig 4 Effect of pre or posttreatment with dexamethasone upon the cathepsin D activity of normal or ischemic myocardium In cats given vehicle myocardial ischemia resulted in 40 per cent decrease in the cathepsin D activity of ischemic ventricle relative to adjacent normal myocardium Pretreatment with dexamethasone reduced the loss of cathepsin D activity to 16 per cent within ischemic myocardium Posttreatment with glucocorticoid prevented the loss of lysosomal hydrolases in acute myocardial ischemia Values are means ± S E M for the number of samples shown on each bar

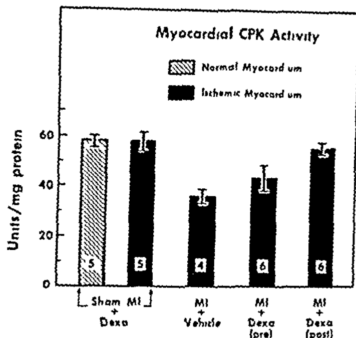


Fig 5 Effect of pre or posttreatment with dexamethasone upon the myocardial CPK activity of normal or ischemic myocardium All values are means ± S E M Numbers at the bottom of each bar indicate the number of myocardial samples studied Ischemic myocardial tissue obtained from vehicle treated cats (MI + vehicle) shows a 40 per cent decrease when compared with adjacent normal left ventricle Posttreatment of cats with dexamethasone prevented the decrease in the CPK activity of ischemic heart tissue

asone and other glucocorticoids failed to exhibit significant vascular or inotropic effects

The similarity of the hemodynamic response of ligated cats was also reflected in the early electrocardiographic changes evident in these cats Marked elevation of the S T segment occurred at 20 to 60 minutes in all groups of cats subjected to coronary artery ligation indicating comparable degrees of initial myocardial injury [13] Although cats given the vehicle for dexamethasone or pretreated with the glucocorticoid maintained similarly elevated S T segment voltage after five hours posttreatment of cats with dexamethasone was associated with a reduction in the S T segment elevation at that time Thus administration of dexamethasone one hour after coronary artery ligation had a beneficial effect as assessed by the reduction of the S T segment elevation in the early phase of acute myocardial ischemia

The ineffectiveness of pretreatment with dexamethasone in reducing the S T segment elevation may be related to the plasma and tissue levels of the glucocorticoid at the time when ischemic myocardial cells began to undergo irreversible damage (i e about two hours after occlusion) [14] Thus pretreatment with dexamethasone results in degradation of the steroid so that inadequate concentrations are present within the ischemic portion of the myocardium at the critical two hour period In contrast posttreatment with dexamethasone provides a high level of glucocorticoid two hours after occlusion the time at which the rate of cellular damage is increasing as indicated by the steep rise in plasma CPK activity of untreated cats

Determination of myocardial CPK activity of normal and ischemic tissue indicated that the observed alterations in plasma CPK activity in MI cats actually reflected loss of myocardial CPK These findings also suggest that posttreatment with dexamethasone was more effective than pretreatment in preventing loss of CPK activity from ischemic tissue Similar results were obtained with regard to myocardial cathepsin D activity Dexamethasone given after coronary artery ligation also prevented the loss of cathepsin D activity from ischemic myocardial tissue more effectively than pretreatment with the same dose of dexamethasone

The 40 per cent loss of myocardial lysosomal

hydrolase activity within ischemic myocardium agrees closely with the findings of Ricciutti[2,15] in dogs not only in quantity but in rate of loss Thus Ricciutti measured comparable loss of lysosomal hydrolase activity within four hours after coronary artery occlusion

Our results indicate that the loss of myocardial lysosomal hydrolase activity within ischemic myocardium can be significantly reduced by administration of pharmacologic doses of dexamethasone Furthermore these results are consistent with the hypothesis that dexamethasone stabilizes myocardial cellular or subcellular membranes within the ischemic myocardium or at the border of the evolving infarct The membrane stabilizing action of the glucocorticoid suggests a mechanism for the infarct reducing effect of other glucocorticoids reported previously[1,3]

Summary

Dexamethasone exerted no significant hemodynamic effect in sham operated cats or in cats subjected to acute myocardial ischemia However the glucocorticoid did normalize elevated S T segments toward pre ischemic values and prevented much of the increase in plasma CPK activity following coronary artery ligation Moreover dexamethasone prevented loss of CPK activity and restricted the loss of lysosomal hydrolase within ischemic myocardial tissue These data indicate that lysosomal disruption is an early consequence of myocardial ischemia and that treatment with dexamethasone prevents the loss of myocardial lysosomal and cellular enzymes as reflected in normalization of the ECG and plasma CPK activity of ischemic cats In this way dexamethasone may act to retard the spread of the developing infarct within the ischemic myocardium

The authors wish to acknowledge the expert technical assistance of Mrs Ann Cibb and Mr Robert Stickley during the course of this investigation We are also grateful for the generous gift of dexamethasone from Dr Ingeborg Schultze of the Merck Institute of Therapeutic Research West Point Pa

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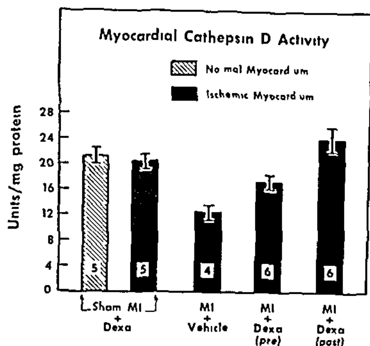


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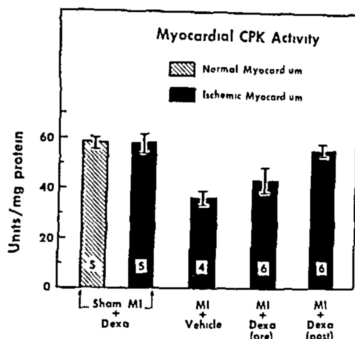


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The 40 per cent loss of myocardial lysosomal

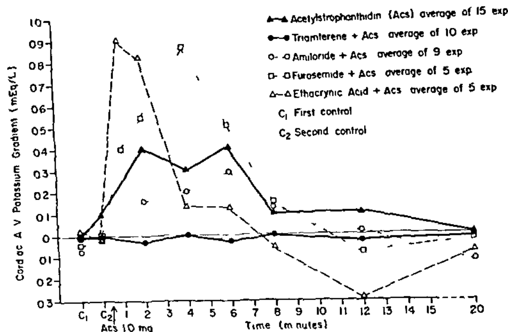


Fig 1 Cardiac A V (coronary sinus–femoral artery) potassium gradient (milliequivalents per liter) after acetylstrophanthidin (1 mg) alone and in combination with potent diuretics and potassium sparing agents

a cuffed endotracheal tube with a Harvard respirator whose tidal volume and rate were adjusted to the dog s weight The dogs were hydrated with 250 ml of isotonic saline Serial Lead II electrocardiograms were obtained with a direct writing electrocardiograph

Acetylstrophanthidin was infused through an indwelling venous catheter at a rate of 100 μg per minute by means of a constant infusion pump The infusion was continued until the onset of digitalis toxicity as evidenced by A V dissociation nodal tachycardia or ventricular tachycardia A series of three acetylstrophanthidin infusions were given at 2 5 hour intervals The amount of acetylstrophanthidin required to produce each toxic arrhythmia was noted

Arterial blood samples obtained prior to each infusion were collected in heparinized tubes centrifuged immediately and the plasma separated and frozen They were analyzed for sodium and potassium by flame photometry (Beckman Photometer Model DU) and for magnesium and calcium by atomic absorption spectroscopy (Perkin Elmer Model 214) Blood samples were replaced with equal volumes of saline

Triamterene was placed in solution by finely grinding 200 mg of powdered triamterene in a test tube Then 40 ml. of distilled water was added slowly with continued stirring Lastly approximately 2 ml of 8 5 per cent lactic acid was added dropwise until the solution became a clear transparent yellow with only minimal amounts of small particles visible to the naked eye The solution was kept warm until injection *directly* into a venous catheter as triamterene is *insoluble in a saline solution* The triamterene 400 mg was then administered intravenously in divided doses (200 mg initially then four doses of 50 mg at 15 minute intervals) during the 60 minute period prior to the third and final acetylstrophanthidin infusion

Group II Extending the toxic dose and increasing the inotropic action of acetylstrophanthidin Fourteen adult mongrel dogs with an average weight of 20 kilograms were anesthetized and ventilated as in Group I Acetylstrophanthidin was infused three times at 2 5 hour intervals as in Group I and the arrhythmogenic dose noted Left ventricular pressure left ventricular dp/dt aortic pressure and electrocardiogram were monitored during each acetylstrophanthidin infusion with an Electronics for Medicine four channel cathode ray tube monitor and recorder Model IR 4C Left ventricular pressure was measured with a Model SF1 Statham catheter manometer and left ventricular dp/dt obtained by using a Model RCD RC differentiator Aortic pressure was measured by placing an

Increasing the inotropic effect and toxic dose of digitalis by the administration of antikaliuretic drugs—further evidence for a cardiac effect of diuretic agents

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James Greco, M D
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Other investigators have shown that the co administration of potassium chloride with a digitalis glycoside antagonizes the arrhythmogenic effect of digitalis without altering its inotropic action Williams, Klocke, and Braunwald[1] concluded that 'the suppression of ouabain induced arrhythmias by potassium chloride does not depress the positive inotropic action of this glycoside and permits the administration of additional amounts of the glycoside which actually produces a further increase in contractile force Although the mechanisms whereby potassium salts suppress digitalis arrhythmias have not been precisely defined, it has been suggested that this may be accomplished by modifying the effect of digitalis on the transmembrane action potential or possibly by displacing digitalis from carrier sites on the cell membrane[2]

Several investigators have suggested an etiologic relation between the loss of myocardial potassium induced by digitalis glycosides and the development of digitalis arrhythmias[3-6] Prior studies in our laboratory, have shown that antikaliuretic drugs not only affect tubular electrolyte transport but also have a direct cardiac effect[7] We demonstrated that triamterene abolishes the increase in cardiac A V potassium difference induced by acetylstrophanthidin and probably blocks the egress of myocardial potassium induced by digitalis glycosides Another potassium sparing agent, amiloride, had a similar but lesser effect Contrariwise, the acetylstrophanthidin induced increase in cardiac A V potassium difference is augmented by the potent kaliuretic and diuretic drugs furosemide and ethacrynic acid (Fig 1) Other work in our laboratory has shown that the potassium sparing drug, amiloride, antagonizes certain electrophysiologic changes induced by acetylstrophanthidin[8]

This current investigation was undertaken to determine whether the cardiac effects of these potassium sparing drugs, triamterene and amiloride might extend the toxic dose of acetylstrophanthidin (i e, permit the administration of larger doses of acetylstrophanthidin before the onset of digitalis arrhythmias) and thereby permit the development of increased inotropic effect before the onset of arrhythmias

Methods and materials

Group I Extending the toxic dose of digitalis by the administration of triamterene Studies were performed in 12 adult mongrel dogs whose average weight was 20 kilograms Anesthesia was induced by giving 25 mg per kilogram of Pentothal sodium intravenously Additional doses were given as needed to maintain anesthesia The dogs were ventilated with 100 per cent oxygen through

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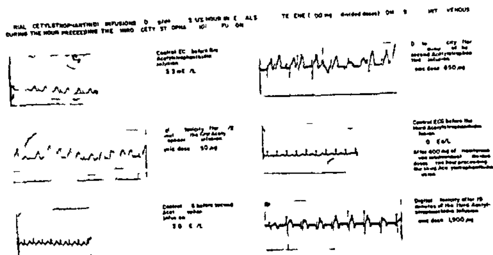


Fig 3 Serial acetylstrophanthidin infusions (100 μg per minute) at 2.5 hour intervals Triamterene (400 mg in divided doses) administered intravenously during the hour preceding the third acetylstrophanthidin infusion

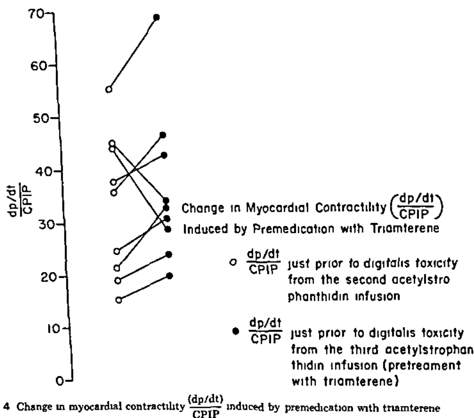


Fig 4 Change in myocardial contractility $\frac{(dp/dt)}{CPIP}$ induced by premedication with triamterene

sion (Fig 2) [9] Therefore the second infusion is considered to be the control infusion to determine the effect of the potassium sparing drug administered prior to the third acetylstrophanthidin infusion The administration of triamterene before the third acetylstrophanthidin infusion resulted in an increase in the toxic dose in *all* dogs The average response was a 110 per cent extension of the toxic dose i e 51 μg per kilogram to 108 μg per kilogram (Fig 2) A typical study is illustrated in Fig 3

Group II In the group of nine dogs which received triamterene the average dose of acetyl strophanthidin required to produce a toxic

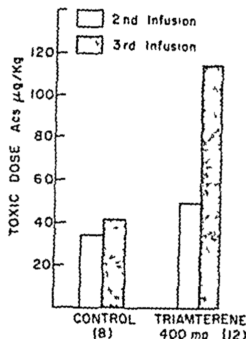


Fig 2 Modifying the toxic dose of digitalis by a direct cardiac effect of triamterene

NIH No 7 catheter in the aortic root and connecting it to a Statham pressure transducer Model P23D6 Arterial blood samples were obtained prior to each infusion and analyzed for sodium, potassium, calcium and magnesium as in Group I

As other investigators have suggested, we felt that the relation between the left ventricular dp/dt and the *simultaneously* developed pressure *during the course of isovolumic contraction or the* dp/dt at the highest common peak developed isovolumic pressure (CPIP) provides a more accurate measure of the effect of drugs on contractility than just the maximum rate of rise of the left ventricular pressure (peak dp/dt)[8]

Nine animals received triamterene (400 mg) intravenously during the hour prior to the third *acetylstrophanthidin infusion and five other ani*mals received 100 mg of amiloride during the same period The relation between left ventricular dp/dt and developed pressure (instantaneous left ventricular pressure minus left ventricular end diastolic pressure) was obtained at 10 milli second intervals during the isovolumic phase of left ventricular contraction and recorded at a paper speed of 100 mm per second The $\frac{dp/dt}{CPIP}$ was determined in the control period before each acetylstrophanthidin infusion and just prior to digitalis toxicity The $\frac{dp/dt}{CPIP}$ is the ratio of left ventricular dp/dt to simultaneously developed peak isovolumic pressures common to the second and third acetylstrophanthidin infusions (CPIP)

The change and percentage increase in $\frac{dp/dt}{CPIP}$ from pre acetylstrophanthidin infusion to arrhythmia observed during the second infusion was compared with the change and percentage increase observed during the third (post triamterene or amiloride) acetylstrophanthidin infusion The dp/dt was always determined at the peak developed isovolumic pressure common to all four measurements Measurements were *determined during the control period preceding* each acetylstrophanthidin infusion and just prior to the onset of the acetylstrophanthidin induced arrhythmia The isovolumic contraction phase was judged to extend to the opening of the aortic valve—the point at which ventricular pressure equaled aortic pressure The relation of dp/dt to developed pressure in the control period and *during interventions was determined as the* average of four consecutive cardiac cycles

Results

No significant changes in serum electrolytes were observed between samples taken prior to the second infusion and those obtained prior to the third infusion The mean serum electrolytes prior *to the second infusion were sodium 140 mEq per* liter, potassium, 3 7 mEq per liter calcium, 3 8 mEq per liter, and magnesium, 1 3 mEq per liter The mean serum electrolytes prior to the third infusion were sodium 140 mEq per liter potassium, 3 6 mEq per liter, calcium 3 9 mEq per liter, and magnesium, 1 3 mEq per liter Triamterene and amiloride caused a *transient drop in blood pressure and contractility* which returned approximately to control levels prior to the onset of the third acetylstrophanthidin infusion except in studies No 8 and No 9

Group I The dose of acetylstrophanthidin required to produce arrhythmia in the first infusion varies greatly and therefore is not used for comparative evaluation On the other hand prior *studies in our laboratory* using each dog as its own control, have shown that with this experimental design (serum electrolytes constant and *without pharmacologic intervention*) there is no statistically significant difference in the dose of acetylstrophanthidin required to produce a toxic arrhythmia between the second and third infu

Table I Effect of triamterene on the toxic dose of acetylstrophanthidin and myocardial contractility

Studies	*Toxic dose of Acs (µg/Kg)*		*Per cent change in toxic dose*	*Myocardial contractility $\frac{dp/dt}{CPIP}$ just prior to dig tox*		*Per cent change in $\frac{dp/dt}{CPIP}$*
	Second infusion	*Third infusion*		*2nd infusion*	*3rd infusion (After Tri)*	
1	32 5	57 5	+76 9	3 5 0 / 100 35 10	4 620 / 100 46 20	+29 41
2	27 5	72 5	+164	4 410 / 80 55 12	5 460 / 80 68.25	+23 82
3	17 5	28 75	+64 3	1,536 / 100 15 36	1 984 / 100 19 84	+29 16
4	37 25	62 5	+67 8	2 486 4 / 100 24 86	3 063 6 / 100 30 64	+23 20
5	35 0	45 0	+28 6	1 912 / 100 19 12	2 390 / 100 23 90	+25 0
6	32.5	51 25	+57 7	4 530 / 120 37 75	5 083 / 120 42.36	+12 21
7	20 0	35 0	+75 0	2 577 / 120 21 48	3 917 / 120 32 65	+52 0
8	33 75	80 0	+137 04	5 387 4 / 120 44 89	4 038 8 / 120 33 62	−24 66
9	22 50	27 50	+22 0	4 410 / 100 44 10	2 835 / 100 28 35	−35 71

Acs = cetylstroph thidin d g tox = d gitalis to ity Tri = triamte en

in $\frac{dp/dt}{CPIP}$ produced by the second acetylstrophanthidin infusion was 17 8 per cent but the per cent increase in $\frac{dp/dt}{CPIP}$ produced by the third acetylstrophanthidin infusion (after the amiloride) was 54 6 per cent The average changes observed with amiloride parallel those observed with triamterene but the small sample size and the lack of response in study No 4 preclude statistical significance

Discussion

Several studies have suggested that one of the major causes of digitalis arrhythmias is the loss of cardiac potassium induced by digitalis Grupp and Charles demonstrated that digitalis glycosides impede the re entry of potassium into the cardiac cell during repolarization Glynn[4] suggested that this effect is probably due to the ability of digitalis to inhibit the activity of sodium potassium-dependent membrane adenosine triphosphatase (ATPase) He stated that increased extracellular concentration of potassium may counteract digitalis induced inhibition of membrane ATPase

Regan and co workers[3] showed that the administration of acetylstrophanthidin resulted in a loss of myocardial potassium which preceded the development of arrhythmias[5] Helfant and co workers[6] also demonstrated that digitalis induced arrhythmias are associated with myocardial potassium egress Williams Klocke and Braunwald[1] demonstrated that the suppression of ouabain induced arrhythmias by potassium chloride does not depress the positive inotropic effect

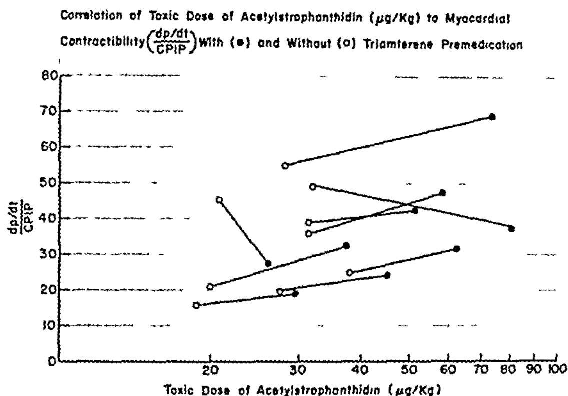


Fig 5 Correlation of toxic dose of acetylstrophanthidin (micrograms per kilogram) to myocardial contractility $\frac{(dp/dt)}{CPIP}$ with (●) and without (○) triamterene premedication

arrhythmia in the second infusion was 28 7 μg per kilogram After receiving 400 mg of triamterene the average dose of acetylstrophanthidin required to produce toxic arrhythmias during the third infusion was 51 1 mg per kilogram This is a 77 per cent increase ($p < 0.01$) in the dose required to produce toxicity (Table I) When the ratio $\frac{dp/dt}{CPIP}$ obtained just prior to digitalis toxicity in the second infusion is compared to a comparable period in the third infusion the seven dogs (Nos 1 through 7 with no myocardial depression prior to the third infusion) showed a mean increase of 27 8 per cent in $\frac{dp/dt}{CPIP}$ ($p < 0.05$) When the two studies (No 8 and No 9) in which myocardial depression induced by triamterene was still present prior to the third acetylstrophanthidin infusion are included a 15 per cent increase in $\frac{dp/dt}{CPIP}$ was noted for these nine studies (Table I Figs 4 and 5)

In the nine studies the mean per cent increase in $\frac{dp/dt}{CPIP}$ from control to just prior to arrhythmia produced by the second acetylstrophanthidin infusion is 15 4 per cent but the per cent increase in $\frac{dp/dt}{CPIP}$ produced during the third infusion (the one in which triamterene facilitated the extension of the toxic dose) is 68 4 per cent (Fig 6 Table II) All comparisons noted were at peak common developed isovolumic ventricular pressures It should be noted that in studies No 8 and No 9 where myocardial depression was noted at the onset of the third infusion there was still a marked rise in the per cent increase in $\frac{dp/dt}{CPIP}$ when the third infusion was compared to the second infusion (Table II) Thus all nine studies showed a measurably greater increase in inotropism induced by acetylstrophanthidin after the administration of triamterene ($p < 0.01$)

In the five studies in which amiloride was administered the toxic dose of acetylstrophanthidin in the third infusion after the administration of amiloride was 45 per cent greater ($p < 0.05$) than the toxic dose required in the second infusion Mean toxic dose in the second infusion was 35 6 μg per kilogram, while the mean toxic dose in the third infusion after 100 mg of amiloride was 52 2 μg per kilogram The mean $\frac{dp/dt}{CPIP}$ at peak developed pressures in the third infusion was 31 per cent greater than observed at a comparable period in the second infusion ($p < 0.05$) (Tables III and IV, Figs 7 8 and 9) The per cent increase

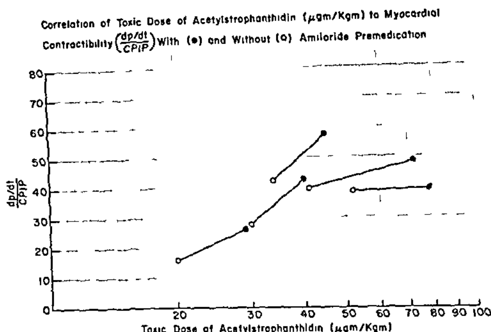


Fig 8 Correlation of toxic dose of acetylstrophanthidin (micrograms per kilogram) to myocardial contractility $\frac{(dp/dt)}{CPIP}$ with (●) and without (O) amiloride premedication

of the glycoside and permits the administration of additional amounts of glycoside which actually produces a further increase in contractile force

We demonstrated in prior studies that the antikaliuretic diuretics triamterene and amiloride have a direct cardiac action and interfere with the digitalis induced egress of myocardial potassium Since the latter is thought to be a major etiologic factor in the development of arrhythmias the current study was performed to determine whether these agents which block the loss of myocardial potassium induced by digitalis can also extend the toxic dose and thereby extend the inotropic effect of digitalis Serial determinations of $\frac{dp/dt}{CPIP}$ at pressures common to the second (control) infusion and the third (potassium sparing drug) infusion demonstrated that premedication with the potassium sparing drugs triamterene and amiloride permitted the administration of significantly more digitalis and consequently the development of increased inotropism before the onset of toxic arrhythmias (Figs 10 and 11)

In these studies heart rate varied Despite slight slowing in rate just before the onset of digitalis toxicity the contractility of the heart increased as determined by $\frac{dp/dt}{CPIP}$ Ordinarily with other factors constant a decrease in cardiac rate would tend to decrease the $\frac{dp/dt}{CPIP}$ Arterial blood pressure was not controlled in these studies in intact animals Although peak ventricular dp/dt is sensitive to changes in inotropism it is also influenced by alterations in blood pressure Since the administration of digitalis glycosides elevates blood pressure it was decided to use the measurement $\frac{dp/dt}{CPIP}$ as a measure of the effect of extended doses of acetylstrophanthidin on myocardial contractility

We concur with the observation of Mason and co workers who stated that the relation between instantaneous dp/dt and the simultaneously developed ventricular pressure during isovolumic systole reflects the contractile state of the myocardium and is independent of arterial pressure Therefore $\frac{dp/dt}{CPIP}$ was used to compare the inotropic effects of varying doses of acetylstrophanthidin

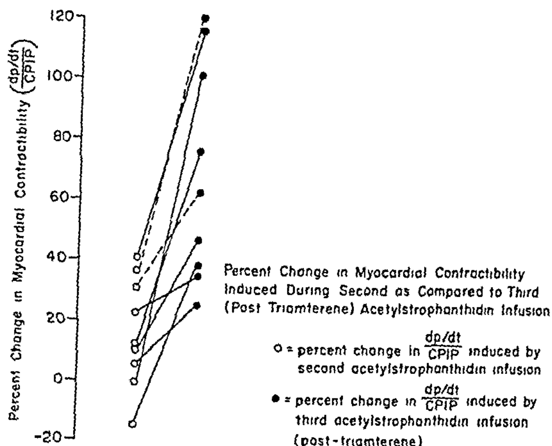


Fig 6 Per cent change in myocardial contractility induced during second acetylstrophanthidin infusion as compared to third (posttriamterene) acetylstrophanthidin infusion

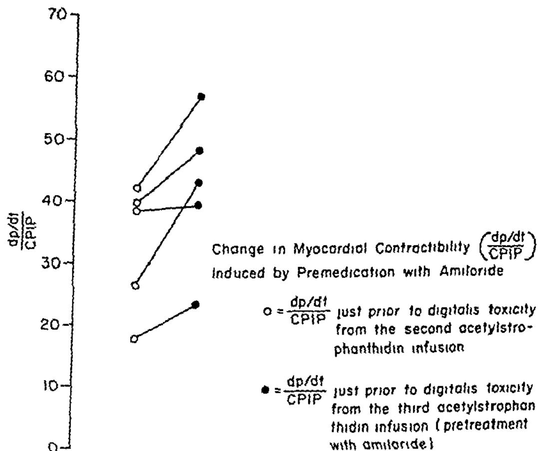


Fig 7 Change in myocardial contractility $\frac{(dp/dt)}{CPIP}$ induced by premedication with amiloride

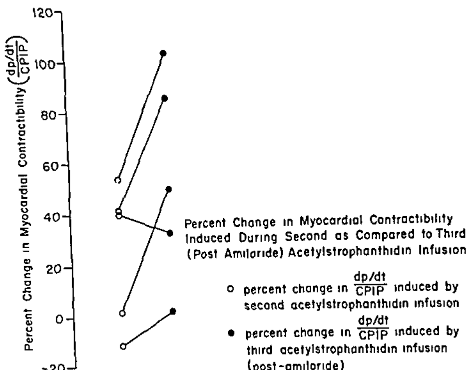


Fig 9 Per cent change in myocardial contractility induced during second acetylstrophanthidin infusion as compared to third (postamiloride) acetylstrophanthidin infusion

of digitalis and thus permit extension of its inotropic activity Although these studies were done in normal animals it is suggested that the administration of these potassium sparing diuretics might contribute to increased safety and increased therapeutic effect of the digitalis glycosides Through their renal tubular effect they block kaliuresis and subsequent hypokalemia *Through a direct cardiac effect they reduce the* digitalis induced loss of cardiac potassium and thus prevent the development of digitoxic arrhythmias

It is suggested that further animal and clinical studies be performed to explore the clinical usefulness of these drugs both in the prevention of digitalis toxicity and in the treatment of refractory heart failure which often requires maximal doses of digitalis with its associated increased inotropic effect

Summary

In prior studies we have shown that the antikaliuretic drugs triamterene and amiloride through a direct cardiac effect reduce the loss of cardiac potassium induced by the administration of digitalis Since loss of myocardial potassium is thought to underlie digitalis arrhythmias this study was performed to determine whether triamterene and amiloride also extend the toxic dose and thus the therapeutic effect of digitalis

In twelve dogs acetylstrophanthidin was infused (100 μg per minute) serially at 2 5 hour intervals Triamterene (400 mg in divided doses) was infused before the third acetylstrophanthidin *infusion This extended the dose required to* produce a toxic arrhythmia by 110 per cent In fourteen additional studies nine dogs received 400 mg of triamterene prior to the third acetylstrophanthidin infusion and five animals received 100 mg of amiloride during the same period

In these fourteen studies not only was the toxic dose of digitalis extended but its inotropic effect $\frac{dp/dt}{CPIP}$ (common peak developed isovolumic ventricular pressure) was also increased

These studies have demonstrated that through a cardiac effect by reducing the digitalis induced loss of cardiac potassium the potassium sparing *drugs triamterene* and amiloride extend the toxic dose of digitalis and thus permit extension of its inotropic activity

Table II Per cent change in $\frac{dp/dt}{CPIP}$ during second infusion compared to third infusion (after triamterene)

Studies	$\frac{dp/dt}{CPIP}$ *Second infusion*		Per cent change	$\frac{dp/dt}{CPIP}$ *Third infusion*		Per cent change
	Control	*After Acs infusion*		*Control*	*After Acs infusion*	
1	$\frac{2\ 562}{100}$ 25 62	$\frac{3\ 570}{100}$ 35 70	+39 34	$\frac{2\ 142}{100}$ 21 42	$\frac{4\ 620}{100}$ 46 20	+115 68
2	$\frac{4\ 515}{100}$ 45 15	$\frac{5\ 512}{100}$ 55 12	+22 08	$\frac{5\ 092}{100}$ 50 92	$\frac{6\ 825}{100}$ 68 25	+34 03
3	$\frac{1\ 664}{80}$ 20 80	$\frac{1\ 408}{80}$ 17 60	−15 38	$\frac{1\ 280}{80}$ 16 00	$\frac{1\ 766}{80}$ 22 07	+37 96
4	$\frac{1\ 998}{80}$ 24 97	$\frac{2\ 220}{80}$ 27 75	+11 13	$\frac{1\ 554}{80}$ 19 42	$\frac{2\ 730\ 6}{80}$ 34 13	+75 75
5	$\frac{1\ 738}{80}$ 21 73	$\frac{1\ 912}{80}$ 23 90	+9 98	$\frac{1\ 630}{80}$ 20 38	$\frac{2\ 340}{80}$ 29 87	+46 56
6	$\frac{3\ 359}{100}$ 33 59	$\frac{4\ 398}{100}$ 43 98	+30 93	$\frac{2\ 984}{100}$ 29 84	$\frac{4\ 840}{100}$ 48 40	+62 19
7	$\frac{2\ 495}{100}$ 24 95	$\frac{2\ 474}{100}$ 24 74	−0 84	$\frac{1\ 835}{100}$ 18 35	$\frac{3\ 690}{100}$ 36 90	+101 08
8	$\frac{3\ 635}{100}$ 36 35	$\frac{4\ 964}{100}$ 49 64	+36 56	$\frac{1\ 839}{100}$ 18 39	$\frac{4\ 015}{100}$ 40 15	+118 32
9	$\frac{3\ 402}{80}$ 45 52	$\frac{3\ 570}{80}$ 44 6	+4 9	$\frac{2\ 163}{80}$ 27 0	$\frac{2\ 688}{80}$ 33 6	+24 4

Acs = acetylstrophanthidin

The studies in Group I demonstrated that premedication with the potassium sparing drug triamterene permits the administration of larger amounts (110 per cent greater) of acetylstrophanthidin before the development of a toxic arrhythmia As mentioned previously we have shown in prior experiments that without the administration of a potassium sparing drug there would be *no significant difference* in the dose needed to produce toxic arrhythmias between the second and third infusion [10]

The studies in Group II demonstrated that this larger dose of acetylstrophanthidin permitted by the administration of triamterene or amiloride resulted in increased contractility In these studies the $\frac{dp/dt}{CPIP}$ just prior to digitalis toxicity in the third infusion was greater than the $\frac{dp/dt}{CPIP}$ just prior to digitalis toxicity in the second infusion As mentioned earlier, developed pressure (left ventricular pressure minus left ventricular end diastolic pressure) was used both in determining the relation of dp/dt to instantaneous isovolumic pressure and in calculating $\frac{dp/dt}{CPIP}$ It should be noted that the dp/dt used in the ratio was that which occurred simultaneously with CPIP and not necessarily peak dp/dt In our studies each animal served as its own control in the evaluation of changes in toxic dose and $\frac{dp/dt}{CPIP}$

Conclusions

These studies have demonstrated that through a cardiac effect, the potassium sparing drugs triamterene and amiloride extend the toxic dose

Table IV Per cent change in $\frac{dp/dt}{CPIP}$ during second infusion compared to third infusion (after amiloride)

Studies	$\frac{dp/dt}{CPIP}$ *Second infusion*		*Per cent change*	$\frac{dp/dt}{CPIP}$ *Third infusion*		*Per cent change*
	Control	*After Acs infusion*		*Control*	*After Acs infusion*	
1	2 079 / 80 25 98	2 117 5 / 80 26 46	+1 84	2 310 / 80 28 87	3 465 / 80 43 31	+50 01
2	2 538 60 / 80 31 73	3 892 5 / 80 48 65	+53 32	2 453 9 / 80 30 67	4 971 4 / 80 62 14	+102 60
3	1,586 1 / 80 19 82	1 418 / 80 17 72	−10 60	1 828 68 / 80 22 85	1 866 0 / 80 23 [illegible]	+2 05
4	2 303 / 80 28 [illegible]8	3 232 / 80 40 40	+40 37	2 262 / 80 28 27	3 009 8 / 80 37 62	+33 07
5	2 321 0 / 80 29 01	3 249 4 / 80 40 61	+40 01	2,321 0 / 80 29 01	4,304 4 / 80 53 80	+85 45

Acs = acetylstrophanthidin

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Table III Effect of amiloride on the toxic dose of acetylstrophanthidin and myocardial contractility

Studies	Toxic dose of Acs (µg/kg) Second infusion	Third infusion	Per cent change in toxic dose	Myocardial contractility $\frac{dp/dt}{CPIP}$ just prior to dig tox 2nd infusion	3rd infusion (After Amil)	Per cent change in $\frac{dp/dt}{CPIP}$
1	30 0	40 0	+33 33	2,118/80 26 47	3,465 0/80 43 31	+63 63
2	33 75	45 0	+33 33	4,231/100 42 31	5 711 8/100 57 12	+34 99
3	20 0	27 5	+37 50	1 418 16/80 17 72	1 866/80 23 32	+31 60
4	52 50	77 50	+47 61	4 646/120 38 71	4 747/120 39 55	+2 17
5	41.25	71 25	+72 72	3 988/100 39 68	4 853/100 48 53	+21 69

Acs = acetylstrophanthidin dig tox = digitalis toxicity Amil = amiloride

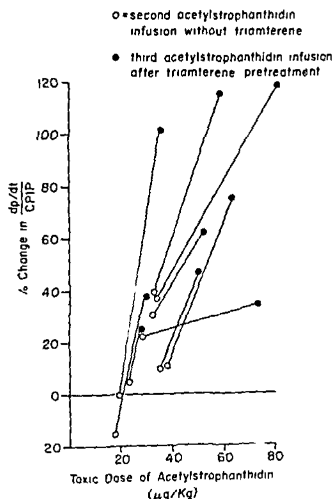


Fig 10 Correlation of toxic dose of acetylstrophanthidin (micrograms per kilogram) to per cent change in myocardial contractility with (●) and without (○) triamterene pretreatment

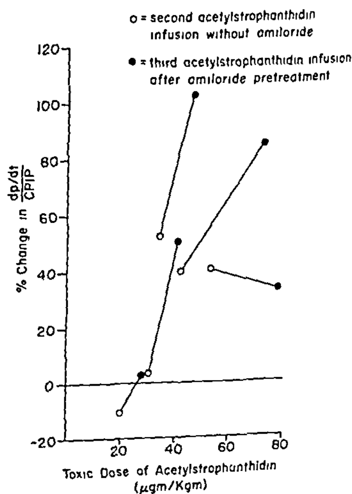


Fig 11 Correlation of toxic dose of acetylstrophanthidin (micrograms per kilogram) to per cent change in myocardial contractility with (●) and without (○) amiloride pretreatment.

Patients with coronary artery obstructive lesions of less than 75 per cent of at least one major coronary artery were excluded Likewise when control exercise hemodynamics were not abnormal the investigation was aborted

These studies were thus performed on eighteen male patients Eight patients received 10 mg of oral ISDN while the other ten were given placebo

Pressures and dye dilution curves were recorded with an Electronics for Medicine multichannel recorder (DR 12) Pressures were measured with Statham P23Db strain gauge transducers The first derivative of the left ventricular pressure curve (LV dp/dt) was measured by an R/C differentiating circuit A Gilford cuvette densitometer was used to determine the cardiac outputs by dye dilution technique using indocyanine green

The following formulas were used

Left ventricular work index =

$$\frac{CI\,(LVSP - LVEDP) \times 13.6}{1000} \quad \text{Kg m/min/M}^2$$

Left ventricular stroke work ind x =

$$\frac{SI\,(LVSP - LVEDP) \times 13.6}{1000} \quad \text{Gm m/beat/M}^2$$

Mean systolic ejection rate =

$$\frac{SI}{SEP} \quad \text{ml/sec/M}^2$$

Tension time index = mean LVSP × SEP × heart rate mm Hg/sec/min

Isovolumic tension index =

$$\frac{\text{LV dp/dt} \times \text{heart rate}}{1000} \quad \text{units}$$

Pressure rate index =

$$\frac{\text{LVSP} \times \text{heart rate}}{100} \quad \text{units}$$

where CI = cardiac index (L/min/M²) LVSP = left ventricular systolic pressure (mm Hg) LVEDP = left ventricular end diastolic pressure (mm Hg) SI = stroke index (ml/beat/M) SEP = systolic ejection period (sec) LV dp/dt = first derivative of the left ventricular pressure (mm Hg/sec)

Each patient provided four measurements on each parameter (resting pre-drug resting post drug exercise pre drug and exercise post drug)

Statistical methods The analysis of covariance was employed to determine whether the resting and exercising hemodynamic effects of 10 mg of oral ISDN are similar to those of placebo The pre drug measurement was regarded as a concomitant variable The covariance analysis procedure was used to adjust the sources of bias in the post drug measurement This procedure enabled us to compare the true effects of the drug on the hemodynamic parameters by utilizing the linear relationship between the pre drug and the post drug measurements In essence the drug effects were compared on the basis of the adjusted means (adjusted to the common pre drug measurements as if both groups were the same before the study medications were given)

Results

Clinical and angiographic data Table I notes the pertinent clinical and angiographic details of patients Their ages ranged from 30 to 55 years (average 46 and 50 years for ISDN and placebo group respectively) Two patients in the ISDN group and three patients in the placebo group had a clinical history and electrocardiographic evidence of prior myocardial infarction In each group the average number of vessels with significant obstruction ($\geq$ 75 per cent lumen narrowing) was 1 6 Left ventriculography showed four normally contracting left ventricles in each group

Exercise induced angina (Table I) Before drug therapy seven out of eight patients (88 per cent) in the oral ISDN group and nine out of ten patients (90 per cent) in the placebo group experienced exercise induced angina Following drug therapy four out of seven patients (57 per cent) were pain free in the ISDN group compared to three out of nine patients (34 per cent) in the placebo group during exercise Two patients in each group (29 per cent for the ISDN group and 22 per cent for the placebo group) indicated chest pain of lesser severity Thus one of seven patients (14 per cent) treated with ISDN showed no change in exercise induced angina compared to four of nine patients (44 per cent) who received placebo

Hemodynamic data

Pre drug exercise hemodynamics (Table II) Changes in left ventricular hemodynamics in exercise induced angina similar to those reported previously by one of the authors (L W)[6] were observed before drug therapy for both the ISDN

Comparative hemodynamic effects of placebo and oral isosorbide dinitrate in patients with significant coronary artery disease

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The therapeutic effectiveness of sublingual nitroglycerin in patients with angina pectoris has been established for almost a century [1] However its beneficial effect is short lived To achieve a more prolonged therapeutic action, various nitrate preparations have been employed These long acting coronary vasodilators have enjoyed considerable clinical use, largely on empirical grounds, and their role in ischemic heart disease still remains controversial [5]

Studies which depend only on subjective evaluation by the patient and where the patient selection is based on clinical grounds rather than on objective angiographic evidence of coronary artery disease are of questionable reliability Investigations designed to rely solely upon objective means such as coronary angiography for the presence of significant coronary disease and hemodynamic measurements for changes introduced by oral long acting nitrates provide a firmer assessment of the role of these drugs in angina pectoris

Methods

Patients were selected from those referred for selective coronary arteriography Patients with evidence of congestive heart failure ventricular aneurysm, valvular or hypertensive heart disease, and obstructive lung disease were excluded Studies were conducted in the fasting state without sedation In all cases nitroglycerin and oral long acting nitrates were discontinued at least 24 hours before the test When possible, patients were exercised the day before the investigation to select a work load which produced angina pectoris Otherwise the work load was estimated by the patient s clinical history Patients were instructed to grade angina as 1+ (mild) 2+ (moderate), 3+ (moderately severe) or 4+ (severe)

Cardiac performance at rest and during supine leg exercise was evaluated by right and retrograde left heart catheterization Exercise was accomplished by using an electrically linked bicycle ergometer After control and three minute exercise measurements were made each patient received, at random, 10 mg of oral isosorbide dinitrate (ISDN) or placebo * Following a period of 60 minutes resting and exercise hemodynamics were again determined In each case extreme care was taken to duplicate the control study accurately The procedure was terminated with a left ventriculography and a selective coronary arteriography Although the study was conducted in a double blind fashion the investigators, in many cases were able to distinguish ISDN from placebo by its hemodynamic effects at rest (decrease in left ventricular and pulmonary artery pressures)

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*Both ISDN (Isordil) and placebo were supplied by Ives Laboratories Inc New York N Y

Table II Mean hemodynamic data

	Placebo				*Isosorbide dinitrate*			
	Rest		*Exercise*		*Rest*		*Exercise*	
	Control	*Drug*	*Control*	*Drug*	*Control*	*Drug*	*Control*	*Drug*
HR	69 ± 9	75 ± 9	107 ± 14	110 ± 14	69 ± 11	78 ± 18	113 ± 10	118 ± 14
LVSP	133 + 17	136 ± 21	164 ± 22	165 ± 20	1?9 ± 15	115 ± 19	16? ± 29	153 ± 28
LVEDP	12 ± 3	11 ± 4	?9 ± 7	?6 ± 5	10 ± 5	6 ± 3	27 ± 11	12 ± 8
PAP	14 ± 2	14 ± 3	31 ± 7	29 ± 8	14 ± 3	10 ± 3	27 ± 7	?0 ± 4
LV dp/dt	1 280 ± 170	1,36? ± 181	2 047 ± 609	2,218 ± ?32	1 701 ± 467	1 626 ± 410	2,539 + 764	2 612 ± 778
CI	3 0 ± 0 6	3 3 ± 0 5	5 6 ± 2	6 2 ± 2	3 1 ± 0 7	2 6 ± 0.5	5 2 ± 1	5 8 ± 1.2
SI	44 ± 8	44 ± 8	?4 ± 15	55 ± 12	44 ± 5	34 ± 6	47 ± 12	49 ± 12
LVWI	5 ± 1 1	5 5 ± 1 2	10 7 ± ?8	11 8 ± 4 7	5 ± 1 4	4 ± 1 4	9 8 ± 3 1	11 1 ± 3 4
SWI	73 ± 19	76 ± 21	101 ± 32	107 ± 33	?2 ± 12	49 ± 9	87 ± 30	94 ± 28
MSER	145 ± 30	149 ± 22	188 ± 52	201 ± 57	145 ± 27	118 ± 16	163 ± 36	176 ± 44
TTI	2,343 + 245	2,517 ± 356	4 112 ± 353	4,258 ± 474	2 306 ± 484	2 144 ± 640	4 46? ± 1 094	3,964 ± 680
PRI	92 ± 11	100 ± 12	173 ± 24	182 ± 31	90 ± 23	91 ± 33	184 ± 45	183 ± ?4
ITI	89 ± 18	102 ± 19	??2 ± 87	252 ± 118	123 ± 46	136 ± 59	288 ± 87	317 ± 109
Asc Ao	99 ± 11	103 ± 8	119 ± 1?	122 ± 11	97 ± 12	91 ± 17	121 ± 19	118 + 24

Abbreviations HR = heart rate (be ts *per minute*) *LVSP* = left ntri ular systolic press *re (mm Hg)* LVEDP = left ventric ılar end diastolic pressure *(mm Hg)* *PAP* = mean pulmon ry artery pressure (mm *Hg*) *LV dp dt* = first derivati of left v ntricular pressure (mm *Hg* sec) *CI* = cardia ind x (L/min./M) SI = st ke index (ml /beat/M) *LVWI* = left ventricular wo k index (Kg m /min /M) SWI = left *ventri ular* trok work ind x (Gm m /beat/M) MSER = m an sy tol *eject on r te* (mL se /M) TTI = tension time index (mm Hg/*sec /min)* *PRI* = pressure rate ind x (units) ITI = iso olumic tension ind *(units)* *Asc* Ao = mean asc nding aort c pres ure *(mm Hg)*

decrease of the left ventricular systolic and mean pulmonary artery pressures was significantly greater with ISDN than with placebo ($p < 0.05$) A more significant reduction of the left ventric ular end diastolic pressure was observed with ISDN than with placebo ($p < 0.01$) The pre-drug measurements of the left ventricular (systolic and end diastolic) and mean pulmonary artery pres sures the cardiac index and stroke index for the ISDN group were somewhat less than the pre drug measurement of the same parameters for the placebo group However the linear relationship between the pre drug and the post drug measure ments was comparable for all parameters

Left ventricular function curve (Fig 2) The patients treated with oral ISDN showed a signif icant shift of the left ventricular function curve to the left and upward compared to patients on placebo ISDN reduced left ventricular dysfunc tion as indicated by prevention of the precipitous abnormal increases in left ventricular filling pres- sure observed during exercise with placebo

Discussion

The efficacy of drug therapy in angina pectoris is difficult to evaluate The unpredictability of the natural history of coronary heart disease the variation in patients symptoms from day to day the subjective nature of the disease the selection of patients based on clinical grounds and the design of the protocol may all contribute to conflicting results among investigators [3,4,7]

The present study was undertaken to overcome some of the aforementioned difficulties All of the patients studied had significant coronary artery disease proved angiographically The exercise work load was individualized in order to produce angina and hemodynamic changes The drug evaluation was performed at the same session and based primarily on direct objective hemodynamic measurements

Our study indicates that 10 mg of oral ISDN has a significant influence on ischemic left ven tricular dysfunction 60 minutes after its oral administration (Fig 2)

Fifty seven per cent of the patients treated with oral ISDN were free of angina compared to 34 per cent of the patients on placebo Only 14 per cent of the patients in the ISDN group showed no change in exercise induced angina compared to 44 per cent of the patients who received placebo That the intensity of angina is not an accurate gauge of the level of left ventricular filling pres sure is evident in Table IV Following oral ISDN administration the absence of angina coincided with normalization of left ventricular filling pres

Table I Pertinent clinical and angiographic details of patients

Case No	Age	Sex	Prev MI	Duration angina	ECG	Heart size	Cor angio R	Cor angio LAD	Cor angio LC	LV angio	Exercise Work load (watts)	Exercise Angina Control	Exercise Angina Post drug
Oral isosorbide dinitrate 10 mg													
1	30	M	No	6 mos	ST changes	Normal	75	50	40	Normal	75	1+	0
2	43	M	Yes	15 mos	Old ant & inf MI	Minimal enlargement	95	80	50	Apical dyskinesia Post wall akinesia	75	4+	2+
3	55	M	Yes	5 yrs	Old ant MI	Minimal enlargement	75	85	65	Apical dyskinesia	50	2+	0
4	46	M	No	2 yrs.	ST changes	Normal	50	95	0	Ant wall hypokinesia	50	3+	0
5	46	M	No	3 yrs	Normal	Normal	85	0	95	Normal	75	2+	2+
6	54	M	No	18 mos	ST changes	Normal	65	75	90	Normal	100	2+	1+
7	42	M	No	3 yrs	Normal	Normal	80	50	40	Normal	50	0	0
8	52	M	No	10 yrs	Normal	Normal	90	95	75	Post wall hypokinesia	50	1+	0
Oral placebo													
9	54	M	Yes	5 yrs	Old ant MI	Normal	0	95	0	Ant wall hypokinesia	75	2+	2+
10	43	M	Yes	4 yrs	Old inf MI	Minimal enlargement	90	60	75	Post wall akinesia	75	2+	2+
11	54	M	No	8 yrs	Normal	Normal	65	95	75	Normal	25	4+	4+
12	43	M	No	2 yrs	Normal	Normal	85	60	0	Normal	75	1+	0
13	50	M	No	3 mos	Normal	Normal	80	30	30	Normal	50	0	0
14	43	M	Yes	4 yrs	Old ant MI	Normal	60	95	85	Apical akinesia	40	2+	3+
15	53	M	No	2 yrs	Normal	Minimal enlargement	40	100	75	Apical dyskinesia	50	3+	2+
16	53	M	No	6 mos	Normal	Normal	100	0	0	Post wall akinesia	25	1+	0
17	50	M	No	2 yrs	Normal	Normal	60	95	50	Ant wall hypokinesia	25	1+	0
18	54	M	No	2 yrs	Normal	Normal	80	80	80	Normal	25	4+	3+

Abbreviations Prev = previous MI = myocardial infarction Cor Angio = coronary angiogram LV Angio = left ventricular angiography R = right coronary artery LAD = left anterior descending coronary artery LC = left circumflex coronary artery ant = anterior post = posterior inf = inferior
Numbers for Cor Angio indicate percentage of lumen narrowing
Grading of angina 1+ = mild 2+ = moderate 3+ = moderately severe 4+ = severe

and placebo groups A precipitous rise in left ventricular end diastolic and mean pulmonary artery pressures an increase in heart rate and cardiac output commensurate with the degree of exertion a rise in left ventricular systolic pressure and left ventricular first derivative, and corresponding changes in other derived parameters were noted

Effects of placebo on exercise hemodynamics (Table II) Exercise hemodynamic effects of placebo showed a 2 to 3 mm Hg decrease in left ventricular end diastolic and pulmonary artery pressures Although these changes are significant ($p < 0.05$), the left ventricular end diastolic pressure remained significantly above the normal range (26 mm Hg) The other parameters remained unchanged

Effects of 10 mg of oral ISDN versus placebo in the resting state (Table III and Fig 1) There was a statistically significant difference between 10 mg of oral ISDN and placebo in terms of reduction of the left ventricular (systolic and diastolic) and mean aortic pressures ($p < 0.05$) A significantly greater reduction ($p < 0.01$) was seen in the following parameters mean pulmonary artery pressure cardiac index stroke index left ventricular work index stroke work index and mean systolic ejection rate Both drug groups were relatively comparable in terms of hemodynamic performance in the initial resting period The results of the covariance analysis show that both drug groups were comparable in terms of the linear relationship between the pre drug and the post drug measurements

Effects of 10 mg of oral ISDN versus placebo during exercise (Table III and Fig 1) The

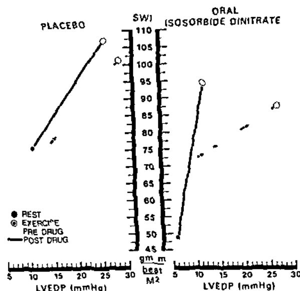


Fig 2 Left ventricular function curve The stroke work index (SWI) is plotted against the left ventricular end diastolic pressure (LVEDP) Note the shift to the left with oral isosorbide dinitrate

oral ISDN did appear to be objectively beneficial As reported by one of the authors (L W)[6] exercise ischemic left ventricular dysfunction usually precedes the subjective complaint of angina Angina may not materialize if significant ischemia is not sustained long enough to induce it

Changes in exercise capacity with oral ISDN were not evaluated An increased exercise capacity however is conceivable in those patients given oral ISDN who remained free of angina and who maintained normal left ventricular filling pressure during exercise The patients on placebo who remained free of angina showed significant elevation of the left ventricular filling pressure

Our study was not specifically designed to evaluate the influence of drug dosage on the hemodynamic parameters and therefore the possibility of altering the exercise left ventricular dysfunction with higher doses of ISDN in the patients who maintained abnormal left ventricular filling pressures after 10 mg of ISDN cannot be assessed

Summary

Comparative hemodynamic effects of placebo and 10 mg of oral isosorbide dinitrate were studied in patients with significant coronary artery disease ($\geq$ 75 per cent lumen narrowing) proved angiographically Isosorbide dinitrate or

Table III Hemodynamic effects of 10 mg oral isosorbide dinitrate (ISDN) in patients with coronary artery disease

	Rest Adjusted Mean		Exercise Adjusted Mean	
	Placebo	ISDN	Placebo	ISDN
HR	74 46	77 80	113 00	114 88
LVSP	134 05	116 94†	164 64	1u3 82†
LVEDP	11 0?	6 73†	25 02	13 10‡
PAP	14.25	9 75‡	28 23	20 8?†
LV dp/dt	1 504 38	1 426 17	2 433 42	2 304.26
CI	3 29	2 54‡	5 95	6 06
SI	44 29	33 64‡	53 21	51 86
LVWI	5 57	3 81‡	11 42	11 65
SWI	75 61	49 48‡	101 66	100 17
MSER	149 14	118 08‡	191 07	188 66
TTI	2 502 83	2 160 97	4 316 46	3 889 79
PRI	99 54	92 07	187 44	176 33
ITI	117 13	114 25	284 64	271 22
Asc Ao	101 92	91.35†	122 04	117 33

Adjusted to a common pre-drug measurement
†S gnificant at 0 05 level.
‡S gnificant at 0 01 level.
Abbreviations Same as in Tabl II

Table IV Left ventricular filling pressure and exercise induced angina

	Exercise				
	Work load	Control		Post drug	
Case No	(watts)	Angina	LVEDP	Angina	LVEDP
Oral isosorbide dinitrate 10 mg					
1	75	1+	15	0	4
2	75	4+	50	2+	22
3	50	2+	19	0	5
4	50	3+	3?	0	8
5	75	2+	22	2+	23
6	100	2+	24	1+	13
7	50	0	18	0	6
8	,0	1+	32	0	18
Oral placebo					
9	75	2+	24	2+	21
10	75	2+	30	2+	30
11	25	4+	41	4+	36
1?	75	1+	40	0	30
13	50	0	24	0	28
14	40	2+	32	3+	21
15	50	3+	25	2+	23
16	25	1+	25	0	2?
17	25	1+	23	0	20
18	25	4+	28	3+	25

LVEDP = Left v ntricular end-diastolic pressure (mm Hg)
Grading of angina 1+ = mild 2+ = mod r te 3+ = moder tely severe 4+ = severe

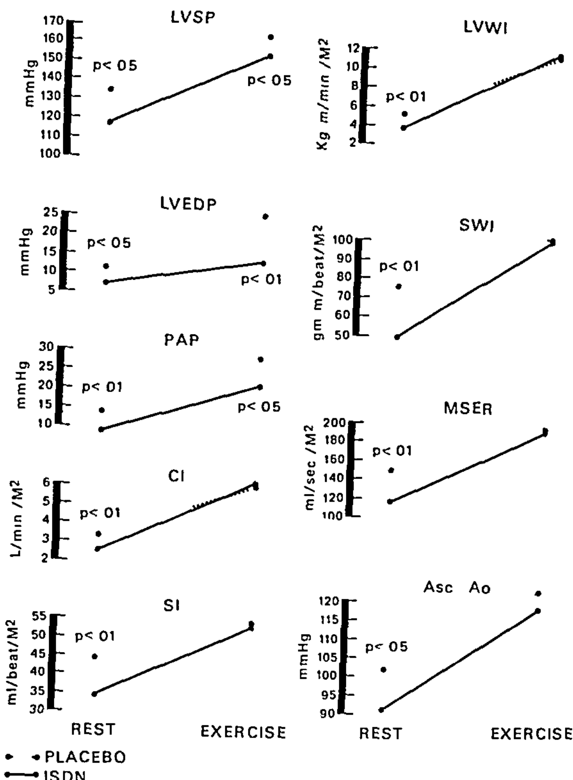


Fig 1 Summary of statistically significant measurements at rest and during exercise between oral isosorbide dinitrate (ISDN solid line) and placebo (dashed line) LVSP = left ventricular systolic pressure LVEDP = left ventricular end-diastolic pressure PAP = mean pulmonary artery pressure CI = cardiac index SI = stroke index LVWI = left ventricular work index SWI = stroke work index MSER = mean systolic ejection rate Asc Ao = mean ascending aortic pressure

sure This was not observed with placebo One patient in each group did not experience angina during the investigation In both patients identical work loads had induced angina the day prior to the study Left ventricular filling pressures were elevated in both Oral ISDN decreased the exercise left ventricular filling pressure from 18 to 6 mm Hg whereas in the patient who received placebo the left ventricular filling pressure rose from 24 to 28 mm Hg Subjectively no difference could be demonstrated between oral ISDN and placebo in these two patients Nonetheless the

Atypical phonocardiographic presentation of a patient with congenital aortic insufficiency

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The clinical and phonocardiographic findings of aortic regurgitation are straightforward and are surprisingly consistent whatever the etiology may be Recently we had the opportunity to study a case which revealed some puzzling auscultatory features

Case report

A man ?4 years of age was admitted to the Veterans Administration Hospital in Cleveland on Sept 14 19 1 for cardiac evaluation The discharge examination from the Air Force in June 19 1 revealed a diastolic murmur presumably due to aortic regurgitation He lived a normal life and denied any history of scarlet fever rheumatic fever or syphilis Because of difficulties in obtaining life insurance he was admitted for cardiac catheterization

His family history was noncontributory Physical examination revealed an alert thin patient His pulse rate was 75 beats per minute and regular His blood pressure was 114/ 6 mm Hg Neck veins were not distended and the lungs were clear to percussion and auscultation The apical impulse was active and located in the fifth left intercostal space at the midclavicular line Heart sounds were normal A loud snapping ejection sound was heard in both infraclavicular fossae A loud protodiastolic click followed by a high pitched blowing diastolic decrescendo murmur grade III/IV was heard in the second right intercostal space and along the left sternal border The peripheral pulses in the upper and lower extremities were equal The carotid pulse was bounding but no other peripheral arterial features of aortic incompetence were observed The remainder of the physical examination was within normal limits

Laboratory findings Complete blood count urea nitrogen fasting blood sugar glutamic oxaloacetic transaminase cholesterol uric acid and chest roentgenogram were normal The resting electrocardiogram (ECG) was within normal limits Simultaneous recording of external phonocardiogram (PCG) with right carotid pulse tracing (CPT) (Fig 1) was recorded An ejection sound was recorded at the third left intercostal space at the left sternal border 30 msec after the beginning of the carotid upstroke Th two major components of the second sound (A and P) are also clearly seen A prominent protodiastolic click (DC) occurs 60 msec after A? and is followed by a high medium frequency (100 to 500 c p s) decrescendo diastolic murmur This diastolic click occurs 10 msec after the 0 point and precedes the peak of the rapid filling wave of the left apex cardiogram (ACG)

Following premedication with 100 mg of Seconal a right and left cardiac catheterization was performed using the right brachial artery and its companion vein Pressures in the right side of the heart were normal Left heart catheterization revealed a normal left ventricular pressure of 110/80 mm Hg No systolic gradient across the pulmonic or aortic valve or diastolic gradient across the mitral valve were recorded

A left ventriculogram was performed in a 30 right anterior oblique position and showed a normal end-diastolic volume Myocardial contractions were extremely vigorous and effected complete ventricular emptying with a normal end systolic volume The mitral valve opened normally There was no evidence of left ventricular outflow tract obstruction or mitral insufficiency

An aortic root angiogram was performed in a 60 left anterior oblique position This demonstrated mild aortic insufficiency with some unusual features While there was regurgitation of contrast material almost immediately after valve closure this appeared to be maximal slightly later in diastole The regurgitant stream was seen as a small jet of contrast material which was also unusual in that the jet was directed eccentrically It appeared to originate from the anterior commissure between the right and left coronary cusps and was directed even more anteriorly rather than vertically in the outflow tract It was thought that this slightly delayed and eccentric regurgitant stream could be consistent with a cusp prolapse occurring slightly after the initial valve closure None of the valve leaflets could be clearly identified as demonstrating prolapse A second possibility is that of a fenestration in an aortic leaflet. An intracardiac phonocardiogram was recorded using a No 6 F Stveltingis single lumen phonocatheter No murmur or protodiastolic click were recorded in the right ventricle Intracardiac phonocardiogram

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placebo was given to eight and 10 patients, respectively in a double blind fashion Cardiac performance at rest and during supine leg exercise was evaluated before and 60 minutes after drug administration In the resting state, isosorbide dinitrate compared to placebo *significantly reduced* the left ventricular (systolic and diastolic), mean pulmonary artery and mean aortic pressures, cardiac index, stroke index, left ventricular work index, stroke work index and mean systolic ejection rate Isosorbide dinitrate also significantly reduced left ventricular (systolic and diastolic) and mean pulmonary artery pressures during exercise This study indicates that 10 mg of isosorbide dinitrate has a significant influence on ischemic left ventricular dysfunction 60 minutes after its oral administration

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nent is a pulmonic protodiastolic click This click was found in patients with pulmonary hypertension or increased pulmonary blood flow due to left to right shunts [7]

This case presents an unusual protodiastolic click probably originating from the aortic valve The click was not recorded in the right ventricle Its maximum recording was above and below the aortic valve and it was followed by a diastolic murmur The aortogram showed a moderate regurgitation of dye which appears to be maximal slightly after the beginning of diastole These findings may explain why the click and the murmur do not start with the closure of the aortic valve It was thought that this delayed and eccentric regurgitant stream could be consistent with a cusp prolapse or fenestrated valve The possibility of artifacts produced by an intracardiac catheter was excluded in our case because of a similar recording which was obtained by external PCG Furthermore it was easily heard by the examiner

The differentiation between this aortic protodiastolic click and the mitral opening snap or the third sound is based on the fact that this sound does not coincide with the 0 point or the peak of rapid filling wave of the left apex cardiogram It is not pulmonic or right ventricular in origin because it was not recorded in the right ventricle

It is possible that this aortic protodiastolic click is the same as the x vibration found by Wiggers [3] Orias and Braun Henendes and Rappaport and Sprague

A search of the literature failed to reveal any reports of similar auscultatory findings

Summary

A patient with congenital aortic regurgitation in whom there was an abnormal aortic protodiastolic click and mid and late diastolic murmur is described

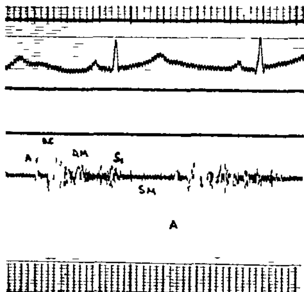


Fig 3 Intracardiac phonocardiogram of the aorta (above aortic valve) with simultaneous (L) electrocardiogram showing the aortic diastolic click followed by a prominent diastolic murmur (All the recordings were obtained using the same sensitivity)

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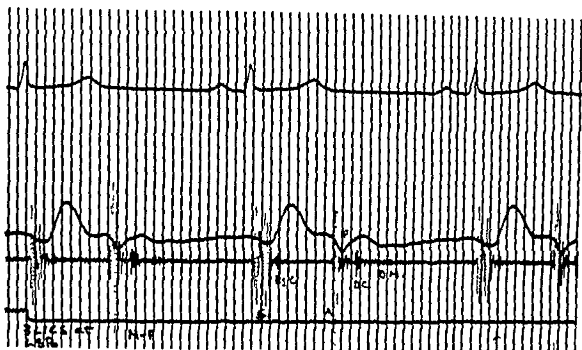


Fig 1 External phonocardiogram recorded over third left intercostal space (3 LICS) with simultaneous electrocardiogram (L) and carotid pulse tracing showing the protodiastolic click followed by a diastolic murmur

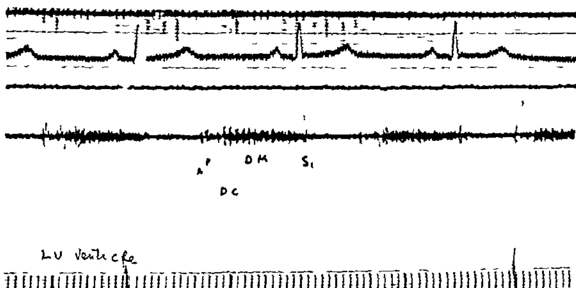


Fig 2 Intracardiac phonocardiogram obtained in the outflow tract of the left ventricle (below aortic valve) with simultaneous L_2 electrocardiogram showing the aortic protodiastolic click followed by a diastolic murmur

of the left ventricle revealed a very prominent protodiastolic click which was followed by a diastolic murmur occupying mid and late diastole The murmur became more prominent as the catheter was withdrawn from inflow to outflow tract (Figs 2 and 3) reaching a maximum intensity above the aortic valve (Fig 3)

Discussion

The normal second sound consists of two separate components which are related to closure of the two semilunar valves[1] and varies with respiration between 40 and 80 msec[2]

In addition to these two components of the second sound other vibrations (x and y components) have been noted[3] The x component occurs in the early or middle portion of the protodiastolic period[3] This component was thought to be a vibration produced by the relaxation of the aortic and ventricular walls as systolic contraction ceased[4,5] *In an experimental study* in dogs Mori and co workers[6] found a y component following the pulmonary component by 40 to 120 msec The vibration was recorded in aortic and pulmonary intravascular phonocardiograms as well

The mechanism of production of the y component is uncertain Coelho and Faleiro[7] were able to correlate and to suggest that this y compo

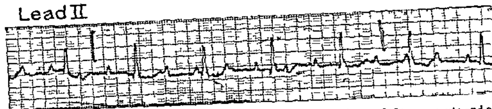


Fig 1 Rhythm strip (Lead II) showing complete heart block with an atrial rate of 124 per minute and a ventricular rate of 5. per minute The QRS is wide (0 12 second) suggesting that the escape is idioventricular



Fig 2 View of the left ventricular outflow tract and aorta of the fixed heart Arrow points to the scar at the base of the aortic and th aortic leaflet of the mitral valve



Fig 3 Summit of the ventricular septum showing a small artery with muscular hyperplasia of media and musculo elastic hyperplasia of intima with marked narrowing Arrows point to small artery Weigert van Gieson stain × 45

Valves and pars membranacea The annulus of the mitral (Fig 4) and aortic valves and the pars membranacea was thickened by fibrous tissu No evidence of active inflamma tion was present

Conduction system

SA NODE Some thi kening of the intima of the nodal artery was present but no appreciable narrowing The SA node was otherwise normal

APPROACHES TO SA NODE Some atrial cells showed cyto plasmic va uolization and there was a slight infiltration with mononuclear cells The arterioles and small arteries showed thickening as described in the myocardium

APPROACHES TO THE A V NODE Moderate mononuclear cell infiltration was present with vacuolar degeneration of subendocardial cells The ramus septi fibrosi showed intimal thickening and slight narrowing As the ramus septi fibrosi approached the A V node (Fig 5) it showed moderate narrowing

A V NODE. A slight infiltration of mononuclear cells was present with slight to moderate fibroelastosis

A V BUNDLE, PENETRATING PORTION Fibroelastosis was moderate here and vacuolar degeneration marked

A V BUNDLE BRANCHING The right side of the bundle showed moderate to marked fibroelastosis (Fig 6) The junction of the l ft part of the bundle with the left bundle branch was almost completely replaced by fibroelastic tissue as it was pushed aside by fibrous tissue in the summit of the ventricular septum (Fig 7) At the bifurcation there was a circular

The conduction system in rheumatoid arthritis with complete atrioventricular block

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Rheumatoid arthritis of the peripheral type, or the ankylosing spondylitis type, with complete atrioventricular (A V) block[1-11] or other conduction disturbances[12-18] has been sporadically reported Very few conduction system studies have been done in these cases[3,7,9,17,18] The present report deals with a comprehensive serial section study of the conduction system in a case of the *peripheral type of rheumatoid arthritis* with complete A V block

Clinical review

The clinical aspect of this case has been previously reported and will be briefly recapitulated here

This was a *52 year old man who had typical peripheral* rheumatoid arthritis for 5 to 6 years before he developed complete heart block with Stokes Adams seizures The electrocardiogram showed complete A V block with widened QRS (Fig 1) The patient received prednisone intermittently until a few months before the heart block developed at which time the medication was discontinued A pacemaker was implanted but failed after five months a second pacemaker was implanted and failed after 11 months The patient died following an episode of irreversible pacemaker induced ventricular tachycardia

From the Congenital Heart Disease Research and Training Center Hektoen Institute for Medical Research and the Departments of Pathology Northwestern University Medical School Pritzker School of Medicine University of Chicago Abraham Lincoln School of Medicine University of Illinois The Chicago Medical School University of Health Sciences Loyola University Stritch School of Medicine Chicago and Cardiology Service Veterans Administration Hospital and the University of Louisville School of Medicine Louisville

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Postmortem examination

Heart

Gross examination The heart was slightly enlarged weighing 470 grams *with thickened attached pericardium and* segment of aorta Both ventricles and the left atrium were somewhat hypertrophied and the *left atrium was also* somewhat enlarged The tricuspid and mitral valves were diffusely thickened The aortic valve was somewhat thickened at the base but the noncoronary cusp was especially thickened throughout A white plaque was present on the ventricular aspect of the aortic leaflet of the mitral valve at the junction of the posterior commissure with the central fibrous body (Fig 2) The coronary arteries showed no appreciable narrowing

Microscopic examination

Methods The sinoatrial (SA) node and its approaches were serially sectioned and every tenth section was retained The *approaches to the A V node* the A V node the A V *bundle* and the bundle branches up to the region just proximal to the muscle of Lancisi were serially sectioned and all sections were retained The remainder of the bundle branches through the region of the moderator band were serially sectioned and every tenth section was retained The remainder of the heart was cut into blocks and two sections were taken from each block In the complete serial sections every fifth section was stained with Weigert van Gieson and the remainder with hematoxylin and eosin stains All the other sections were alternately stained with hematoxylin and eosin and with Weigert van Gieson stains *In this manner a total of 7 430 sections* were studied This method of study has previously been reported Normal hearts of this age have previously been studied as controls

Myocardium There was muscular hyperplasia of the medial and musculo elastic hyperplasia of the intima with narrowing of some of the small arteries and arterioles (Fig 3) This was more *marked in the summit of the ventricular* septum where there was also fibrosis and small scars *Although the myocardium in the* distal part of the atrial septum showed an infiltration with mononuclear cells no active myocarditis was present elsewhere in the myocardium

An arteriole is in this paper considered to be 0 3 mm or less up to the level of the capillaries

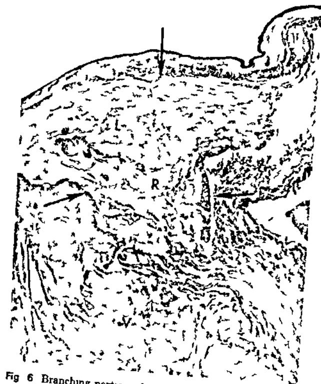
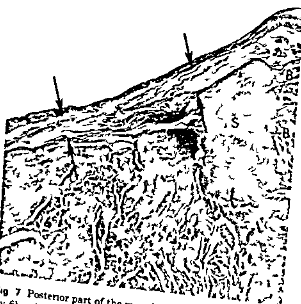


Fig 6 Branching portion of A V bundle showing fibroelastosis of right side Weigert van Gieson stain × 45 Arrows point to the bundle R = right side of bundle L = left side of bundle and V = ventricular septum



ig 7 Posterior part of the main left bundle branch replaced y fibroelastic tissue as it is pushed aside by mass of fibrous ssue at summit of ventricular septum Hematoxylin-eosin ain × 45 Arrows point to LBB S = scar at the summit of he ventricular septum V = ventricular septum and = branching portion of A V bundle



Fig 8 A V bundle at bifurcation showing circular scar pressing on bundle and its junction with LBB Weigert van Gieson stain × 45 Arrows point to circular mass of fibrous tissue B = A V bundle LBB = left bundle branch and V = ventricular septum

spread of the inflammatory and fibrotic process from the aortic lesion to the aortic valve to the pars membranacea central fibrous body and thus to the conduction system (2) in the periph eral type of rheumatoid arthritis there may be direct involvement of the conduction system by rheumatoid granulomas or involvement of the conduction system by extension of the granulo matous inflammation from the base of the aortic or mitral valves

In our case we are dealing with a somewhat different mechanism of genesis of the block from those reported in the literature There are no active granulomas present in this case but plaque formation in the spot where active granu lomas have previously been reported[1, 2] We may consider these fibrotic patches at the summit of the ventricular septum in our case as the end result of healed granulomas pressing on the branching bundle the bifurcation and the begin

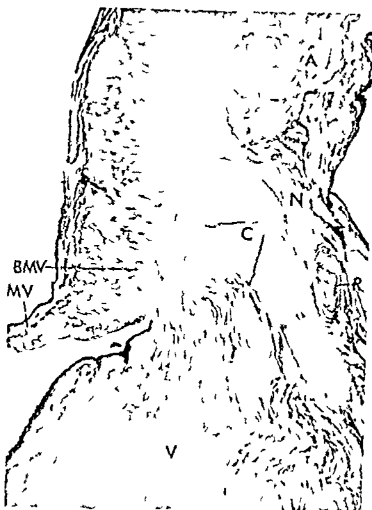


Fig 4 Marked fibrous thickening of base of mitral valve Weigert van Gieson stain × 45 MV = mitral valve BMV = base of mitral valve C = central fibrous body V = summit of ventricular septum N = A V node r = ramus septi fibrosi and A = atrial septum

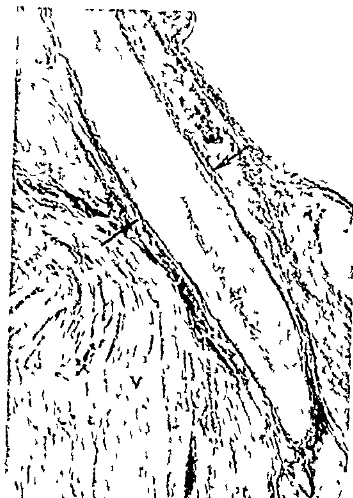


Fig 5 Longitudinal section of A V nodal artery Arrows point to the zone of narrowing This section is from complete serial sections of this artery which show proliferation of the intima throughout sections in this area Weigert van Gieson stain × 45 V = ventricular septum

hyalinized mass of fibrous tissue which aided in the interruption and also impinged upon the right side (Fig 8)

LEFT BUNDLE BRANCH (LBB) As mentioned above this was cut off from the main bundle and was replaced by fibroelastic tissue More peripherally it was intact but showed marked vacuolar degeneration The latter was maximal in the peripheral Purkinje cells

RIGHT BUNDLE BRANCH (RBB) The first part showed marked fibroelastosis and arteriolar thickening and narrowing (Fig 9) Vacuolization of the cells was marked The fibroelastosis was less marked in the second and third parts but the vacuolization was equally intense

Discussion

Rheumatoid heart disease has been recognized since 1944 [22] It may take on several forms [1 18 22 33] In one type there is an aortitis which spreads to the aortic valve to produce aortic insufficiency This type is seen especially in the ankylosing spondylitis variety In another type there are rheumatoid granulomas in the epicardium myocardium, and the annulus and ring of the mitral aortic and sometimes tricuspid valves This type is seen especially in the peripheral variety In a third type there is a nonspecific adhesive pericarditis myocarditis, and thickening of the base and edge of the mitral and aortic valves This type is also found in the peripheral variety of rheumatoid arthritis and may be a healed form of the second type All types may be associated with either an active or healed arteritis of the small coronary arteries and arterioles

Complete A V block is uncommon in rheumatoid arthritis However, lesser degrees of block are not rare [12 16 18] This is true of both rheumatoid spondylitis and the peripheral type of rheumatoid arthritis

From the few cases in which conduction system studies have been made in A V block in this disease it is apparent that the following mechanisms can be involved in the block (1) in rheumatoid spondylitis with aortitis, there may be a

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Fig 9 Beginning of first part of right bundle branch showing considerable fibroelastosis and arteriolosclerosis Weigert van Gieson stain × 45 Arrows point to right bundle branch V = ventricular septum

ning of the bundle branches This produces fibro elastic separation of the LBB from the branching bundle and produces fibroelastosis of the right side of the branching bundle and the beginning of the RBB These effects are reinforced by the ischemic effects of thickening and narrowing of the arterioles and small arteries to the conduction system which may be considered as due to a healed arteritis The A V block is thus subjunc tional and manifested by the wide QRS com plexes The vacuolar degeneration in the bundle of His and the bundle branches is considered to be acute, and hence not related to the chronic A V block

The question arises as to whether the changes in the vessels are due to cortisone administration which may produce an arteritis The changes found in our case have been reported in rheuma toid arthritis without cortisone administration, and hence they are more likely part of the disease process itself

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ities but also of previous experiences and of the cultural pattern

The flow of nerve impulses from the active muscle to the brain may be perceived as pain or as fatigue The fatigue is recognized as a progressive weakness of the contracting muscle and in the realization by the subject that the voluntary muscle does not respond to his will Fatigue occurs commonly when the load is negligible or when its magnitude approaches the limit of the strength of the contracting muscles These findings indicate that the cerebral interpretation of the impulses arriving from the contracting muscles may be quite variable When the perception is of pain or of fatigue the exercise comes to a halt

The symptoms reported by patients with the diagnosis of angina pectoris[2] or intermittent claudication are remarkably variable Almost the entire range of the words used for pain listed by Melzak and Torgerson[3] has been reported by patients with arterial disease These terms include deep spreading radiating boring piercing stabbing crushing pressing vise like squeezing pulling aching drawing hurting choking burning suffocating distressing excruciating intolerable and tiring or simply as fatigue

The discomfort is continuous and persistent and independent of individual contractions or relaxations When its source is in skeletal muscle it is usually referred to the region of the contracting muscle or to adjacent joints When the source is in the heart the pain is referred to the anterior chest wall often with radiation to the neck or jaw and to the ulnar distribution of the left arm These variations in description introduce significant difficulties into the analysis of the data obtained on normal subjects engaged in voluntary muscle contraction Evaluation is even more complex when the source of the disturbance is in the viscera

Related muscle pains Unaccustomed exertion generates a dull aching muscle pain that may persist for days even though the blood supply is presumably normal This may be attributed to overload and injury of the muscle and its tendons When the exercise becomes habitual hypertrophy of the muscle and its attachments reduces the likelihood of damage and the pain gradually diminishes and disappears Trauma to muscles produces a boring deep pain which is probably due to direct injury to muscle and nerve cells and not solely to a restricted blood supply Intermittently recurrent pain has been attributed to spasm For example tension headaches have been attributed to spasm of the occipital muscles Cramps are painful contractions of the muscles especially in the elderly these pains can sometimes be controlled by stretching the affected muscles or by the administration of quinine

Other forms of pain associated with muscle contraction are those due to inflammatory processes such as myositis or tendonitis Inflammation of epiphysial and related connective tissue sheaths may give rise to muscle pain Pains arising in the joints may also be interpreted as muscle pain The surprisingly common costochondral tenderness of Tietze s syndrome is often misinterpreted as angina pectoris Some of these sources of pain can be identified by pressure on the site of reported pain Reassurance in such cases can sometimes eliminate the symptom completely These complex factors can introduce ambiguity into the study of muscle pain

Problems in analysis

Despite the objectivity of the disturbances in muscle that lead to pain clinical evaluation is remarkably difficult especially in angina pectoris Some investigators insist that data on such pain which by definition is subjective cannot be objectivized This attitude has stifled research on these potentially lethal mechanisms

Numerous studies have been directed to medical or surgical means for the control of such symptoms but few of these studies have been properly controlled Some of the reported results on the part of investigators may have been due to the wishes of the physician and to the deep concern and fears of the patient The resulting anxieties can greatly augment the discomfort It is well appreciated that an enthusiastic approach offered by the physician or experimenter can through purely psychologic bases greatly alleviate fear and reduce the apparent pain

Such factors may have contributed to the recurrent disappointment with some of the surgical procedures that for various intervals have had vogue in the therapy of angina pectoris Surgical procedures have included pericardial poudrage ligation of the coronary venous sinus coronary endarterectomy mammary artery ligation insertion of the mammary arteries into slits cut into the ventricular myocardium and

Review

Pain associated with muscular activity

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Acute pain in contracting muscles is a frequent experience in patients with arterial disease It is also a common experience in normal subjects In normal subjects the sensation usually results from prolonged or repeated contraction of a voluntary muscle against an unaccustomed load A heavy valise, carried at first with almost complete ease, soon generates an annoying sensation of discomfort in the arm and shoulder muscles The discomfort gradually progresses becomes moderate and then severe Finally the ache or fatigue becomes so intolerable that the load must be released even if this means that the train or plane is missed The discomfort or pain is so prepotent that it can force the cessation of the muscular work even in the face of the threat of death Thus an individual trapped in a situation in which he must hold on to a ledge or a rope must soon release his hold even though he knows that a fatal fall will result

Intermittent claudication The circumstances outlined above for pain in voluntary muscles have similarities to the pain in intermittent claudication angina pectoris, and intestinal angina Intermittent claudication occurs in patients whose femoral arteries are severely narrowed as in arteriosclerosis obliterans[1] These patients can walk only a limited distance before leg muscle discomfort forces them to stop After an interval of rest even in the standing position they can resume their walk but the discomfort returns quickly after walking a shorter distance To hide their embarrassment these patients become 'window shoppers who stand quietly before a store window until they can again comfortably resume their stroll The severity of the disease process has been evaluated in terms of the distance walked between the stops this distance becomes shorter as arterial narrowing becomes progressive In the end stages of arteriosclerosis obliterans the patient can walk only a few steps before another rest period becomes imperative

Angina A similar disturbance is experienced when the involuntary muscles of the heart or of the intestines receive an inadequate blood flow However, discomfort, pain, or fatigue cannot inhibit the recurrent contractions of these organs The symptoms may therefore become progressively more severe Angina pectoris ('suffocation in the chest') and intestinal angina are commonly associated with narrowed arteries that impede the delivery of an adequate flow of blood to the contracting organs When blood supply is inadequate recurrent contraction injures the muscle cells, and ultimately can lead to their necrosis The serious general consequences of such localized tissue damage have led to many studies of the clinical phenomenon of infarction

Like other discomfort the sensation of severe pain impresses itself so vividly upon the attention of the patient that his search for relief becomes a primary activity If the pain becomes intolerable he may exhibit progressive irritability and aversive behavior He begins to thrash about and finally he will project strong feelings against persons or objects in his environment Relief of the discomfort eliminates the emotional disturbance within a few seconds and the episode is quickly forgotten

The discomfort

Pain inducing stimuli subserved by various nerve impulses are modulated and interpreted by higher mechanisms This modulation is determined by the functional structure of the higher centers which select and abstract this information out of the total input Thus the words called forth to describe the discomfort represent interpretations not only of sensory and affective qual

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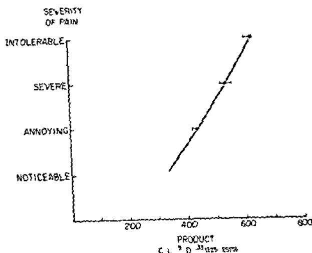


Fig 2 Relation of product of number of contractions (C) square root of the load (L) and the cube root of the duration of each contraction (D) plotted against the reported severity of pain (vertical axis) in young subjects with no known cardiovascular disease Blood flow to the arm was occluded by a tourniquet The severity of the pain increases with the product The dots represent averages the horizontal bars represent one standard deviation The data were obtained from several different loads and durations of contraction

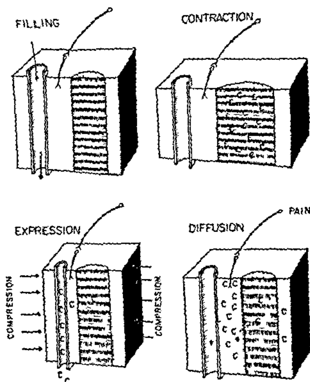


Fig 3 Concept of role of muscular contraction in production and removal of pain catabolite In upper left a representation muscle fiber and a capillary are enclosed with extracapillary fluid in a fibrous connective tissue capsule In upper right muscle fiber produces catabolites (C) during active contraction as length of capsule is shortened In lower right catabolites diffuse out of muscle fiber into extracapillary fluid High concentrations of catabolite adjacent to nerve fiber stimulate nerve impulses which on reaching the brain induce the sensation of pain Pain is referred to site of the contracting muscle In lower left contraction of adjacent fibers compresses the capsule squeezing extracapillary fluid and most of the contained catabolite out of the capsule and back into the blood circulation In upper left capsule no longer compressed fills with ultrafiltrate It is appreciated that phenomena shown at upper right and those shown in lower left may occur simultaneously

number of contractions performed prior to the development of pain or of the inability to continue because of fatigue varies with the strength of the muscles involved the load that must be lifted the frequency and the duration of the contractions the square root of the load and the cube root of the duration of each contraction The product of these factors is remarkably constant for each degree of severity of pain (Fig 2)

Hypothesis We have operated on the hypothesis that each contraction of an ultimate contractile unit (sarcomere) generates a stoichiometric quantity of a toxic catabolite or pain substance in the muscle fiber (Fig 3 *A* and *B*) The relationship between depolarization and contraction in the production of the catabolite is illuminated in studies on the heart Normally every fiber in the heart is depolarized in every beat (all or none law) yet the tendency to the development of pain is known to vary with load i e with the tension developed in each beat The quantity of the catabolite produced in each beat is therefore independent of the depolarization process The number of contractile elements that participate in a given contraction of the heart is apparently the determining factor in the concentration of the pain substance and this appears to vary with the total tension developed by the heart during that beat as it ejects its contents[8] The mechanical tension developed by the heart in a given beat also correlates with its oxygen uptake The total tension and the oxygen uptake per minute also vary with the number of beats per minute These data suggest that the production of the catabolite may be related to the actual process of shortening in those sarcomeric units that are involved in the contraction

The work that can be performed before the appearance of intolerable pain varies inversely with the strength of the contracting muscle as

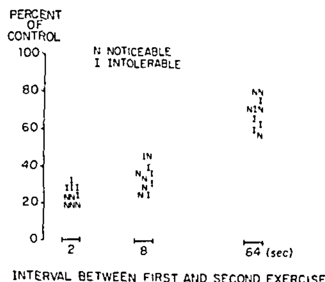


Fig 1 The number of contractions performed in the first test was considered to be 100 per cent The number of contractions performed in the second test is shown The number of seconds during which the cuff was deflated prior to the resumption of exercise is shown in the horizontal axis (2 8 and 64 seconds) *N* is the per cent of contractions performed prior to onset of noticeable pain *I* is the per cent performed prior to onset of intolerable pain Extrapolation suggests that recovery should be complete in about 10 minutes

currently bypassing a stenotic coronary artery segment with a saphenous vein graft or anastomosis with a mammary artery

Some of the problems inherent in the evaluation of these therapeutic approaches to pain are highlighted by experiences with mammary artery ligation This relatively simple surgical approach to the problems of coronary artery disease and angina pectoris was based on the belief that ligation of the mammary arteries would divert more blood to the adjacent coronary arteries Mammary artery ligations were soon followed by reports of gratifying reductions in the frequency and severity of anginal attacks This question was then properly approached in double blind tests Patients with angina pectoris were carefully studied At the time of the anterior thoracic skin incision a card was drawn to separate the patients into two random groups In one group the mammary arteries were ligated a high percentage of these patients had relief from their complaints of chest pain In the other group only the skin incision was made but the mammary arteries were not ligated, an equal percentage of these patients had relief from their symptoms These findings emphasized that analysis of angina pectoris could founder on the complications introduced by the wishes and anxieties of the patients and of their physicians

Experimental procedures

Although pain is subjective responses to the sensation of pain can be quantified Since skeletal muscle pain can be easily produced this procedure offers a means to assay the pain process The reader can readily examine the facility with which pain can be produced by recurrently flexing and extending the fingers of a hand as rapidly as possible A sensation of discomfort appears in the forearm within 30 seconds Continuation of the exercise causes the discomfort to become progressively annoying

Further contractions usually lead within a minute or two to a sensation of severe local pain or burning and then to such profound weakness fatigue, or pain localized to the region of the contracting muscles, that the exercise cannot be continued

A few seconds of rest relieves the discomfort although a sense of local fatigue may persist for a minute or so A demonstrable pain' residue remains in the affected muscle for a longer period This can be demonstrated by attempting to repeat the exercise after a minute of rest and unimpeded blood flow the discomfort usually recurs after fewer contractions than were performed in the initial test (Fig 1)

Quantification The abnormalities associated with contraction of skeletal muscle can be quantified by having the subject report when the discomfort is noticeable and when it becomes annoying severe or intolerable Inability to continue the voluntary exercise is a useful end point

Controlled randomized tests show that each individual will perform a remarkably uniform number of contractions under standardized conditions and against a given load A measurement with objective characteristics is thereby recorded Tests of this kind are useful not only in estimating the pain tolerance of subjects, and in the evaluation of the reports given by patients concerning the severity of the pain they report as arising from angina pectoris or other pain syndromes but also in the analysis of the mechanisms that produce the pain

Mechanism We have examined the pain associated with muscle contractions by controlling such parameters as load duration and frequency of contraction the arterial or venous pressures the interval between successive contractions the intervals between successive tests etc The

cells and thus can result in higher extracellular concentrations of the catabolite despite the smaller number of contractions (Fig 4)

The catabolite persists in muscle for minutes after exercise has been stopped and blood flow has been reinstituted (Fig 1) This suggests that it is a molecule of significant size The molecular weight of the catabolite is estimated from its apparent rate of diffusion as having a molecular weight of perhaps about 1 000 The catabolite cannot be destroyed locally in the muscle in which it was formed since the discomfort induced by a pain producing exercise persists as long as blood flow is obstructed It apparently must be washed away by the resumption of blood flow through the affected tissue

Toxicity The toxicity of the catabolite appears to result from a destructive local action on membranes As with increases in the local concentration of other toxic materials affected cell membranes are first stimulated The accumulation of sufficient catabolite in a specific site stimulates local nonmyelinated fibers to fire impulses perhaps through a toxic action on the neuronal membrane A sufficiently intense barrage of neurogenic impulses leads to a voluntary cessation of contraction or in some instances to an involuntary cessation of muscle exercise associated with fatigue

Excessive catabolite concentration probably produces severe cellular damage which only the cessation of contractile activity can prevent Evidence for cell damage comes indirectly from two sources that indicate changes in the permeability of the muscle cell membranes Thus excessive muscle exercise increases the permeability of muscle cells to glucose thereby resembling the insulin induced augmentation of muscle cell permeability In phosphorylase deficiency of muscle even mild exercise can produce severe muscle pain in association with the leakage of myoglobin out of the affected muscle cells An acute bout of contractile activity as in wrestling or following an epileptiform convulsion can result in a massive escape of myoglobin The quantity escaping out of the damaged membranes of the muscle fibers may be sufficient to produce myoglobinuria and even renal tubular obstruction with myoglobin crystals

Washout We examined the rate at which the pain inducing catabolite can be eliminated by the blood stream (Fig 1) [b] A tourniquet cuff on the upper arm occluded the blood supply to the contracting muscles When the muscle pain became intolerable or the muscles would no longer contract because of fatigue the cuff was deflated The pain or fatigue was relieved almost at once Reinflation of the cuff then again occluded the blood flow and the hand exercise was resumed The number of contractions that could be performed after a two second interval of blood flow that had provided complete relief from the pain was only about one fourth the number that could be performed in the initial test Thus even though the pain has been relieved a residue of catabolite persists in the muscle This preformed material diffuses out of the muscle fibers during the second bout of exercise and thereby accelerates the rate of appearance of pain Blood flow for eight seconds before reapplication of the cuff and reinstitution of the exercise resulted in an increase in the number of contractions to 40 per cent of the initial number After one minute of blood flow about 75 per cent as many contractions as in the initial test could be performed These data appeared to follow a logarithmic washout curve Complete recovery of the capacity to perform the exercise appeared to require more than 10 minutes of unimpeded blood flow

Intrinsic obstructions to flow Some aspects of the nature of the pain substance can be investigated when there is no extrinsic interference with the blood flow to the muscle as in arm exercise experiments in which no tourniquet is used During each contraction of a muscle the rise in intramuscular pressure compresses the blood capillaries and reduces the vascular conductance (flow/pressure) of the affected bed During the subsequent relaxation blood flow takes place probably in the form of a hyperemia

The ability to continue the exercise varies with the duration of muscle relaxation between successive contractions (Fig 4) [a] In our experiments hand exercise could be continued 15 minutes or longer without the development of significant pain when 40 contractions per minute were performed Increases in the number of contractions per minute to 50 60 and 70 shorten the intervals of muscle relaxation during which muscle blood flow can take place freely and decrease the number of contractions performed prior to the onset of pain

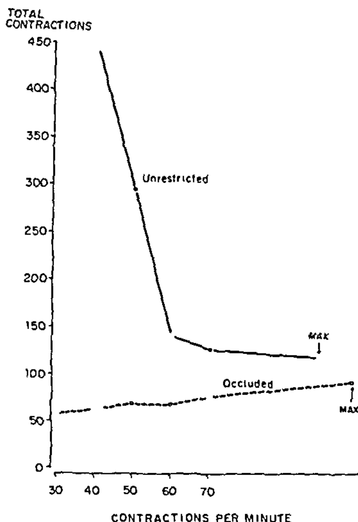


Fig 4 Number of contractions performed prior to fatigue or intolerable pain The frequency of contraction is shown in the horizontal axis The line is extended to the maximal rate that could be performed by each individual The number of contractions (vertical axis) performed when blood flow was unrestricted was indeterminate at slow rates (< 40 per minute) but decreased at faster rates The number that could be performed when a tourniquet occluded the arterial inflow increased with the frequency of contraction The two curves approached a common value at very rapid rates of contraction

measured with a dynamometer (Fig 4) We may assume that the number of units required to produce the tension of each contraction is distributed among the larger number of units in a hypertrophied muscle As a result the amount produced in each sarcomere, per unit of total muscle tension is reduced in a stronger muscle

As long as the catabolite remains inside the muscle fiber there is no conscious recognition of its presence Diffusion of the catabolite out of the cell increases its extracellular concentration When its concentration reaches a threshold value adjacent nerve fibers are stimulated and a train of impulses is initiated (Fig 3 C) Arrival of these impulses in the central nervous system generates the perception of a sense of discomfort, pain, or fatigue As the concentration of the catabolite in the tissue increases, the discomfort that was at first only noticeable and then annoying, becomes severe, and the contractions become progressively weaker Finally the discomfort becomes intolerable

The catabolite Our analysis suggests that the catabolite responsible for pain or fatigue in contracting muscle is a toxic material which must be eliminated from the tissue at any cost

The pain inducing catabolite cannot be lactic acid This conclusion results from the finding that muscle pain tends to be unusually severe and damaging in patients with McArdle s disease a deficiency of the phosphorylase that converts muscle glycogen to lactic acid

Oxygen lack is not the factor that produces the toxic catabolite If the pain were due to lack of oxygen or to the washout of a highly diffusible substance blood flow for one minute should have been more than adequate to restore pre exercise conditions The failure of complete recovery in this interval (Fig 1) indicates that the elimination of the agent responsible for pain depends on other time limited mechanisms Further, tourniquet occlusion of the blood flow into the arm for as long as 20 minutes with the production of severe ischemia has little effect on the number of contractions that can be performed The development or elimination of the pain is unaffected by the breathing of pure oxygen even at three atmospheres (2 200 mm Hg of oxygen) of pressure The pain catabolite is therefore, not directly related to oxygen deficiency

Diffusion Experiments have been performed to evaluate the diffusion of the catabolite Such studies are best performed while the flow of blood to the affected muscles is stopped by the application of an arterial tourniquet to the upper arm These studies have been based on the assumption, as noted above that each contraction of a given strength (number of contractile elements triggered to contract) and of a given duration produces a stoichiometric quantity of catabolite The greater the interval between contractions, the fewer the number of contractions necessary to produce intolerable pain or fatigue Longer intervals between contractions provide more time for diffusion of the catabolite out of the affected

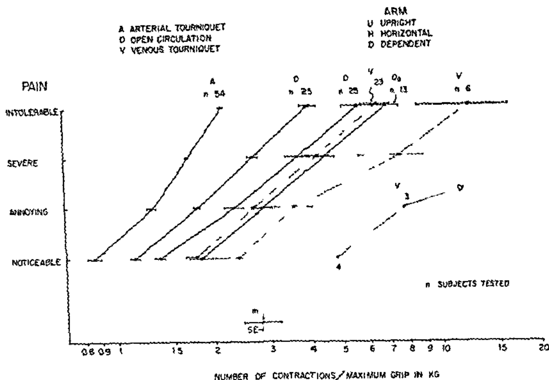


Fig 6 Horizontal (logarithmic) scale gives the number of contractions divided by the strength of the hand in kilograms as measured by a dynamometer Vertical scale gives reported quality of the pain Abbreviations are indicated. The lowest number of contractions was performed when an arterial tourniquet (A) on the upper arm obstructed blood flow (line at left) The greatest number of contractions was performed when a venous tourniquet (V) was on the arm with the arm in the dependent (D) position Intermediate values were obtained when no tourniquet was on the arm (O) The position of the arm is noted in subscripts U H and D (Rodbard S and Farbstein M Journal of Applied Physiology 33 704 1972 Reprinted by permission)

Venous congestion Venous congestion enhances exercise tolerance (Fig 6)[13] This has been demonstrated by inflating a cuff on the upper arm to between 10 to 40 mm Hg The number of hand contractions that can be performed under these conditions may double These findings suggest that venous engorgement of the muscles of the arm facilitates the washout of tissue fluids and their contained catabolite during each contraction This may result from an increased bulk exchange of fluid in the congested contracted muscles

Perception The intensity of the perceived pain is independent of the number or size of the muscle bundles involved Thus pain from a single small muscle bundle may be as severe as pain from a much larger muscle mass or from several simultaneously affected muscles When tourniquets are on both upper arms simultaneous recurrent flexion of the two hands results in findings that the number of contractions performed by each arm working simultaneously is not significantly less than can be performed by each arm in separate tests This is so even though the total quantity of catabolite in the body is twice as great as in the experiments on a single arm This indicates that the stimulus that generates the pain is the local concentration of catabolite Impulses from the exercising muscles therefore do not summate intracranially Instead each muscular locus of the production of pain catabolite appears to have its own central representation or all the impulses go to a common site which permits signals from only one site to pass through the gate to consciousness

Evaluation

If the catabolite is an end product of muscle contraction why is it not simply an innocuous material that may be transported away at the convenience of local mechanisms rather than being a material that can and does threaten life? We must assume that the production of the pain causing substance is a necessary part of the

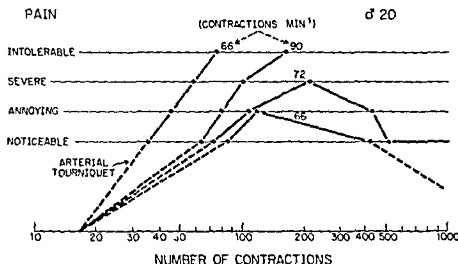


Fig 5 Walk through phenomenon in a male aged 20 Horizontal axis is number of contractions (logarithmic scale) Vertical axis is the reported severity of discomfort or pain in the contracting arm The line at left was obtained with a tourniquet on the upper arm at a contraction rate of 66 per minute Pain was first noticed at 34 contractions and became intolerable at 75 contractions With no tourniquet on the arm 80 contractions were performed prior to noticeable pain At 110 contractions the pain became annoying At 450 contractions the grade of discomfort was reported as only noticeable and shortly after that the discomfort disappeared completely (walk through phenomenon) despite continued contractions to a total of 1 000 At 72 contractions per minute the pain became severe before it returned to the noticeable state At 90 contractions per minute no walk through was observed

These findings are consistent with the thesis that when blood flow is adequate, as occurs during the relatively long intervals of relaxation between successive contractions the catabolite does not accumulate in quantities sufficient to initiate pain or to force the end of the performance At faster contraction rates the decline in the duration of the relaxation interval and in the resulting washout interval is inadequate for the rapid elimination of the pain producing catabolite

Walk through This phenomenon also known as second wind is observed at contraction rates intermediate between a high frequency that produces progressive discomfort to the point of intolerable pain and a slower frequency that can be continued indefinitely In such tests the subject usually reports the appearance of pain and its progression to annoying or even severe qualities after about one minute Continued contractions instead of causing progression of the pain then result in its disappearance and the exercise can be continued indefinitely without its reappearance (Fig 5) This walk through phenomenon may result from the hyperemia associated with the exercise and the resulting more effective washout of catabolite An elevation of systolic pressure, commonly observed during exercise, may also increase blood perfusion

Arterial pressure Since the rate of blood flow appears to be implicated in the elimination of pain the effects of changes in arterial pressure on the generation of pain have been studied [11] To do this we compared the number of contractions that could be performed while the arm was in a position horizontal to the body, with the number performed while the arm was elevated on an arm rest (Fig 6) Maintenance of the arm in the upright position reduces the arterial pressure in the muscles of the forearm by about 25 mm Hg Nearly twice as many contractions could be performed with the arm in the horizontal position than when it was upright Arterial perfusion with the arm upright especially in individuals who are unaccustomed to this position therefore appears to be less effective in eliminating the pain factor from the exercising forearm muscles than when the arm is horizontal

An elevated arterial pressure can be expected to increase the perfusion of the contracting muscle [11] This interpretation is supported by the finding that more contractions can be performed with the arm in the dependent position than in the horizontal or upright positions The arteries in the dependent arm have a higher pressure because of hydrostatic position It is also known that the arterial pressure tends to rise during intermittent claudication [1] This increase in perfusion pressure may increase blood flow and improve the elimination of the catabolite from the fluids of the contracting muscle

Fundamentals of clinical cardiology

Drug interactions in cardiovascular therapy

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Concurrent administration of several drugs has become a common necessity during cardiovascular therapy Because the concomitant use of therapeutic agents can increase the effectiveness of pharmacotherapy and decrease the prevalence and severity of untoward side effects many cardiovascular diseases are best treated with more than *one* drug Furthermore many patients need pharmacologic therapy for more than one cardiovascular problem and may require drug treatment of noncirculatory diseases

Most nonhospitalized patients with cardiovascular diseases receive one or more drugs from therapeutic categories such as cardiac glycosides diuretics antiarrhythmics antihypertensives vasodilators antilipemics anticoagulants analgesics or sedative hypnotic tranquilizers In addition there is much consumption of nonprescription drugs from the last two categories When patients are hospitalized for cardiovascular diseases on acute medical services in the United States they receive a median of 12 drugs during their hospitalization (Fig 1) Almost all such patients are at times treated simultaneously with five or more drugs and some with as many as 15 concurrent drugs[2,3]

When multiple drug therapy is needed and well chosen it should arouse neither concern nor censure On the contrary much of the success of modern pharmacotherapy for cardiovascular diseases is the result of skillful concomitant prescription of more than one drug However simultaneous administration to a patient of several potent drugs demands special knowledge and care on the part of the physician in order to derive the maximum benefit and to prevent occasional serious complications of such therapy

Whenever a patient is treated concurrently with two or more drugs there exists the possibility that their effects will interact Most such interactions are planned by the physician and are beneficial (Table I) They are induced deliberately in order to achieve greater therapeutic effectiveness than is possible with a single drug or to mitigate adverse side effects of an essential drug For example combination therapy of hypertension with a diuretic agent a beta adrenergic receptor antagonist and a peripheral vasodilating drug is far more effective and safe than treatment with maximal doses of only *one* of the drugs Similarly the interaction of propranolol and nitrites can be beneficial in the treatment of angina pectoris[5,6] Diminution of adverse side effects of drugs is exemplified by the concomitant administration of a potassium wasting and a potassium retaining diuretic[7] or of antacids with gastric irritating drugs Planned and useful drug interactions are so common in cardiovascular therapy that hundreds of examples could be cited and they will not be discussed here in any detail The administration of receptor blocking drugs or of less specific antagonists in the treatment of intoxication by cardiovascular drugs also creates a deliberate drug interaction but such pharmacologic treatment of drug toxicity will *not* be considered in this review

Adverse drug interactions

Unfortunately concurrent administration of two or more drugs also sets the stage for adverse drug interactions These unexpected events are far more common than is generally appreciated and have been responsible for much serious morbidity and numerous deaths[8,9] Their incidence increases sharply with the number of drugs coadministered The recognition that such unfor

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contractile mechanism We have suggested that the catabolite is obligatorily formed in the course of the triggering of the shortening of each contractile unit[14] However the catabolite is also a highly toxic material which can produce serious harm to the contractile machinery that forms it Miniscule quantities of the material probably produce highly potent effects

Why should muscle contraction, a fundamental process in animal survival be hobbled by the toxic action of some product of the contraction itself? We may speculate that the diffusion of relatively large toxic molecules posed no problems to the tiny organisms in which contractile mechanisms first evolved The subsequent incorporation of astronomic numbers of contractile units in each muscle cell then introduced problems of elimination of the catabolites generated during contraction

Why does the nervous system not ignore the presence of the pain producing catabolite? We may assume that local accumulation of this material is highly toxic to the tissues

The cell membrane poses a hindrance to diffusion of the catabolite out of the muscle fiber Ideally, cellular permeability must be sufficiently great to permit the catabolite to diffuse freely, while preventing the escape of the myoglobin that is dissolved in the same fluids The catabolite may facilitate its own diffusion by acting on the membrane of the cell in which it is formed The contractile process through its massaging action of the tissue also aids transport out of the cell The volume of extracellular fluid probably affects the concentration of the catabolite at the cell membranes and at the site of local nociceptors The pumping action of the contracting muscle can then operate to squeeze extracellular fluids and their dissolved catabolites back into the blood capillaries (Fig 3)

An adequate vascular bed can produce a stream of blood flow and perhaps of equal importance, mass transport of extracapillary fluid to eliminate the pain catabolite Failure of blood flow because of inadequate perfusion pressure or because of vascular narrowing may permit the local accumulation of toxic concentrations of the catabolite

It appears then that muscle contraction is associated with the production of a slowly diffusible toxic catabolite of significant molecular weight The blood stream normally transports this material away from the muscle cells

Isolation and identification of this substance may provide means for the further elucidation of elements of the contractile process the mechanism of stimulation of nociceptive nerve fibers the inhibition of the toxicity of the substance and the clarification of general problems related to pain and fatigue

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Fundamentals of clinical cardiology

Drug interactions in cardiovascular therapy

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Boston Mass

Concurrent administration of several drugs has become a common necessity during cardiovascular therapy Because the concomitant use of therapeutic agents can increase the effectiveness of pharmacotherapy and decrease the prevalence and severity of untoward side effects many cardiovascular diseases are best treated with more than one drug Furthermore many patients need pharmacologic therapy for more than one cardiovascular problem and may require drug treatment of noncirculatory diseases

Most nonhospitalized patients with cardiovascular diseases receive one or more drugs from therapeutic categories such as cardiac glycosides diuretics antiarrhythmics antihypertensives vasodilators antilipemics anticoagulants analgesics or sedative hypnotic tranquilizers In addition there is much consumption of nonprescription drugs from the last two categories When patients are hospitalized for cardiovascular diseases on acute medical services in the United States they receive a median of 12 drugs during their hospitalization (Fig 1) Almost all such patients are at times treated simultaneously with five or more drugs and some with as many as 15 concurrent drugs

When multiple drug therapy is needed and well chosen it should arouse neither concern nor censure On the contrary much of the success of modern pharmacotherapy for cardiovascular diseases is the result of skillful concomitant prescription of more than one drug However simultaneous administration to a patient of several potent drugs demands special knowledge and care on the part of the physician in order to derive the maximum benefit and to prevent occasional serious complications of such therapy

Whenever a patient is treated concurrently with two or more drugs there exists the possibility that their effects will interact Most such interactions are planned by the physician and are beneficial (Table I) They are induced deliberately in order to achieve greater therapeutic effectiveness than is possible with a single drug or to mitigate adverse side effects of an essential drug For example combination therapy of hypertension with a diuretic agent a beta adrenergic receptor antagonist and a peripheral vasodilating drug is far more effective and safe than treatment with maximal doses of only one of the drugs Similarly the interaction of propranolol and nitrites can be beneficial in the treatment of angina pectoris[5,6] Diminution of adverse side effects of drugs is exemplified by the concomitant administration of a potassium wasting and a potassium retaining diuretic[7] or of antacids with gastric irritating drugs Planned and useful drug interactions are so common in cardiovascular therapy that hundreds of examples could be cited and they will not be discussed here in any detail The administration of receptor blocking drugs or of less specific antagonists in the treatment of intoxication by cardiovascular drugs also creates a deliberate drug interaction but such pharmacologic treatment of drug toxicity will not be considered in this review

Adverse drug interactions

Unfortunately concurrent administration of two or more drugs also sets the stage for adverse drug interactions These unexpected events are far more common than is generally appreciated and have been responsible for much serious morbidity and numerous deaths[8, illegible] Their incidence increases sharply with the number of drugs coadministered The recognition that such unfor

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contractile mechanism We have suggested that the catabolite is obligatorily formed in the course of the triggering of the shortening of each contractile unit [14] However, the catabolite is also a highly toxic material which can produce serious harm to the contractile machinery that forms it Miniscule quantities of the material probably produce highly potent effects

Why should muscle contraction, a fundamental process in animal survival, be hobbled by the toxic action of some product of the contraction itself? We may speculate that the diffusion of relatively large toxic molecules posed no problems to the tiny organisms in which contractile mechanisms first evolved The subsequent incorporation of astronomic numbers of contractile units in each muscle cell then introduced problems of elimination of the catabolites generated during contraction

Why does the nervous system not ignore the presence of the pain producing catabolite? We may assume that local accumulation of this material is highly toxic to the tissues

The cell membrane poses a hindrance to diffusion of the catabolite out of the muscle fiber Ideally, cellular permeability must be sufficiently great to permit the catabolite to diffuse freely, while preventing the escape of the myoglobin that is dissolved in the same fluids The catabolite may facilitate its own diffusion by acting on the membrane of the cell in which it is formed The contractile process through its massaging action of the tissue also aids transport out of the cell The volume of extracellular fluid probably affects the concentration of the catabolite at the cell membranes and at the site of local nociceptors The pumping action of the contracting muscle can then operate to squeeze extracellular fluids and their dissolved catabolites back into the blood capillaries (Fig 3)

An adequate vascular bed can produce a stream of blood flow and perhaps of equal importance, mass transport of extracapillary fluid to eliminate the pain catabolite Failure of blood flow because of inadequate perfusion pressure or because of vascular narrowing may permit the local accumulation of toxic concentrations of the catabolite

It appears, then, that muscle contraction is associated with the production of a slowly diffusible toxic catabolite of significant molecular weight The blood stream normally transports this material away from the muscle cells

Isolation and identification of this substance may provide means for the further elucidation of elements of the contractile process, the mechanism of stimulation of nociceptive nerve fibers, the inhibition of the toxicity of the substance, and the clarification of general problems related to pain and fatigue

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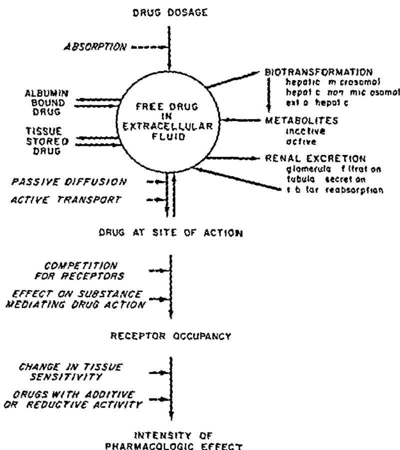


Fig 2 *Schematic representation of potential sites of drug interactions*

drugs requires special caution The number of these drugs is not too large and the precautions to be taken when they are used in multiple drug therapy are not too complex to be remembered by the conscientious pharmacotherapist This review concerns itself only with well documented clinically important drug interactions which substantially influence the effectiveness or safety of cardiovascular pharmacotherapy

Mechanisms of cardiovascular drug interactions

An understanding of the mechanisms by which drugs can influence each other s actions is an essential framework for remembering the occurrence and characteristics of drug interactions These mechanisms are logically divided into two types (Table II) First one drug may change the activity of another by altering its metabolic fate Such pharmacokinetic drug interactions change the concentration of one or both drugs at their sites of action and correspondingly influence the intensity of the pharmacologic effects of the drugs Second drugs can directly influence each other s intensity of action at their active sites Fig 2 shows a schematic representation of the major sites of potential interactions between drugs Many cardiovascular drugs interact with one another and with other drugs at more than one site Pharmacokinetic drug interactions are generally

Table II Mechanisms of cardiovascular drug interactions

A. Modification of drug metabolism
  1 Absorption
  2 Binding at inactive sites
  3 Biotransformation
  4 Excretion
  5 Movement to site of action
B Modification of drug action at active site
  1 Competition for receptors
  2 Effect on substance mediating drug action
  3 Change in tissue sensitivity
  4 Additive or reductive drug activity

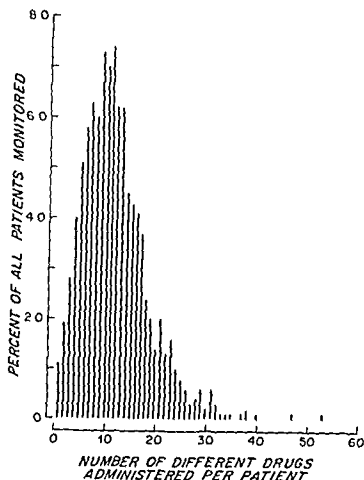


Fig 1 Distribution by number of drugs received of 500 patients hospitalized for cardiovascular diseases on acute medical services of the Massachusetts General Hospital

Table I Clinical classification of cardiovascular drug interactions

- A *Beneficial interactions*
  - 1 Enhancement of therapeutic effect
  - 2 Diminution of untoward effects
- B *Adverse interactions*
  - 1 Decrease of therapeutic effect
  - 2 Production of toxic actions

tunate events can occur with particular drugs has often been long delayed,[11] and it seems certain that some adverse interactions involving cardiovascular drugs still remain to be uncovered. Adverse drug interactions can be responsible for *impairing the action of drugs* thus causing a loss of therapeutic benefits (Table I). Alternatively they can cause toxic drug effects. These are generally intensifications of the usual pharmacologic effects into the toxic range but at times they *consist of a type of toxicity qualitatively different* from the actions of the drugs when administered alone.

It has been possible to postulate an enormous number of potentially detrimental interactions involving cardiovascular drugs. Almost all this activity has taken place during the past decade and has resulted in some highly exaggerated estimates of the clinical implications. In actual fact, most of these putative interactions have not been confirmed in man, have been shown not to occur in man, or lack any importance in the clinical setting. There has been an unfortunate tendency to compile and publish endless lists of drug interactions that are based largely on animal experiments or on anecdotal clinical reports. Results of animal studies cannot be extrapolated to the therapeutic situation because species differences in drug metabolism are profound[13] and because the enormous drug dosages studied in animals are often clinically meaningless. A single speculative interpretation of a complex clinical event does not substantiate it as a drug interaction. Some interactions involving cardiovascular drugs can be demonstrated by sensitive experimental techniques in man but have only a minimal influence on the dose effect relationship of the drugs involved and need not concern clinicians prescribing these drugs. Uncritical compilations of drug interactions serve no useful purpose and have only led to confusion in cardiovascular drug therapy.

There are, however, a sizable number of drug interactions that constitute an important cause of inadequate therapeutic results or of adverse effects during therapy with cardiovascular agents. It could not be otherwise because the therapeutic margin of many cardiovascular drugs, such as cardiac glycosides, anticoagulants and antiarrhythmics, is small and minor increases or decreases in the intensity of their action can lead to therapeutic failures or to important toxicity. Adverse drug interactions involving cardiovascular drugs can catch the physician by surprise but almost all of them are predictable and preventable with sufficient knowledge and foresight.

Drugs that are capable of interacting with adverse results can usually be coadministered safely and effectively if the necessary dosage adjustments are anticipated or instituted promptly. This requires familiarity with the metabolic fate and with the major therapeutic and toxic actions of each drug. Every physician should know the important cardiovascular drugs whose simultaneous administration with other

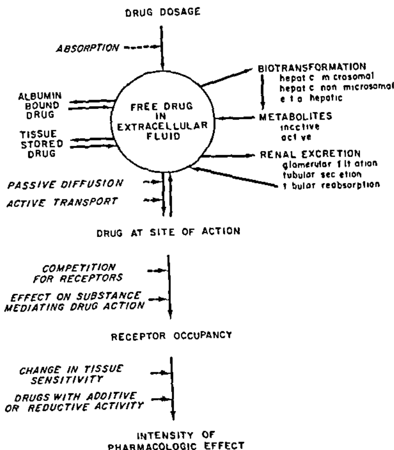


Fig 2 Schematic representation of potential sites of drug interactions

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Table III Interactions affecting gastrointestinal absorption of cardiovascular drugs

1. Change in gastric or intestinal pH (antacids)
2. Change in GI motility (motility stimulants or depressants)
3. Change in GI perfusion (cardiovascular drugs)
4. Interference with mucosal function (neomycin colchicine)
5. Chelation (tetracycline)
6. Exchange resin binding (cholestyramine)
7. Adsorption (charcoal kaolin antacids)
8. Solution in poorly absorbable liquid (mineral oil)
9. Unknown mechanisms (heptabarbital–bishydroxycoumarin allopurinol–warfarin)

more unexpected and subtle than interactions at the site of drug action They are fully predictable only when the processes of absorption distribution binding biotransformation and excretion of each drug are completely understood In contrast, interactions at the site of drug action are usually related to the expected pharmacologic actions of the drugs and are more easily anticipated

It must be emphasized that the mechanisms of some drug interactions are still not understood This is particularly true of interactions that occur only in a small minority of patients exposed simultaneously to the interacting drugs and which therefore presumably involve unusual patient characteristics

Interactions affecting absorption of cardiovascular drugs When several drugs are administered concomitantly by mouth the gastrointestinal absorption of one or more may be altered [14] Both changes in the rate of drug absorption and in the completeness of absorption may be therapeutically important Changes in the rapidity of absorption can influence the therapeutic result when the peak intensity of drug action is important but are of little consequence during chronic drug therapy Changes in the completeness of absorption are always of potential clinical importance because they alter the relationship between dosage of a drug and its average concentration at the site of action [14] Drug interactions in the gastrointestinal tract generally decrease drug absorption, but may increase the bioavailability of poorly absorbed drugs These interactions tend to influence most importantly the gastrointestinal absorption of drugs such as digoxin guanethidine and bishydroxycoumarin that are incompletely or unreliably absorbed even in the absence of interfering substances [14] The magnitude of the change in drug absorption varies with many factors other than the drugs involved including dosage, time relationship between administration of the drugs and patient characteristics Gastrointestinal absorption of some drugs is almost abolished by the oral administration of other drugs within hours

The major mechanisms of drug interactions in the gastrointestinal tract are listed in Table III Since most cardiovascular drugs are weak acids or bases and are absorbed in the nonionized form, their absorption in stomach and intestine is influenced by the luminal pH By shortening gastrointestinal transit time, cathartics can decrease the completeness of absorption of slowly absorbed drugs Drugs which depress gastrointestinal motility, such as opiates ganglionic blocking agents anticholinergics or antacids containing the aluminum ion slow the absorption of most drugs but can increase bioavailability of drugs that are usually incompletely absorbed Cardioactive or vasoactive drugs that change intestinal perfusion or edema of intestinal mucosa may influence drug absorption Drugs that can interfere with normal function of the intestinal mucosa such as neomycin and colchicine apparently decrease bioavailability of some cardiovascular drugs Several therapeutic agents decrease bioavailability of orally administered drugs through physicochemical interactions including chelation, complex formation adsorption, and dissolution in nonabsorbable liquids A few drugs interfere with the intestinal absorption of cardiovascular drugs by mechanisms that are still obscure

Drug interactions can also affect the bioavailability of drugs that are concomitantly administered by the parenteral route *Many drugs are* inactivated or precipitated from solution if they are mixed in syringes or added to infusion fluids prior to administration [15,16] This practice should be avoided unless the absence of in vitro interactions has been clearly established

The rate of absorption of intramuscularly or subcutaneously administered drugs can be importantly influenced by the simultaneous administration of other drugs Cardioactive or vasoactive drugs may change the rate of perfusion at the injection site and correspondingly the rate of absorption The effects on drug absorption rate of the local coadministration of vasodilator or vaso

constrictor drugs have long been documented and clinically utilized

Interactions affecting albumin binding of cardiovascular drugs Many cardiovascular drugs are reversibly attached to inactive sites on serum albumin Binding to albumin decreases the peak intensity of drug action because the albumin bound fraction is pharmacologically inactive [1, 2] On the other hand the duration of drug action is prolonged because the fraction bound to albumin may be protected from biotransformation and cannot be filtered by the glomeruli Table IV shows the degree of albumin binding of some important cardiovascular drugs when their concentration in the serum is in the therapeutic range

Highly albumin bound cardiovascular drugs can be partially displaced from their binding sites by other drugs The ability of a drug to displace another from albumin increases with its concentration in the serum and its affinity for albumin [9] Phenylbutazone and its congeners are the most important displacing drugs but there are many others

When displacement causes decreased albumin binding of a cardiovascular drug and increases its free concentration the intensity of its pharmacologic action is immediately enhanced The partial displacement of a cardiovascular drug from albumin is clinically most consequential if normally only a small fraction of the drug is free and active and if the toxic effects of excessive free drug concentrations are serious Thus the consequences of displacement are most serious for coumarin anticoagulants

The potentiation of the action of a displaced cardiovascular drug is always transient The higher unbound concentration makes more of the drug available for biotransformation or glomerular filtration and the concentrations of total and free drug in the serum fall progressively until a new equilibrium is reached If drug dosage has not been changed the new steady state is characterized by a lower total concentration of the drug the same free drug concentration and the same intensity of action as before the addition of the displacing drug to therapy [2, 9] The sequence proceeds in reverse when a drug which competes for binding sites on albumin is withdrawn Thus altered intensity of cardiovascular drug action due to interference with albumin binding inevitably corrects itself but may cause serious mishaps before it can do so The times required for the development and subsidence of displacement interactions depend on the time course of cumulation and elimination of the drugs involved [22, 3]

Table IV Highly albumin bound cardiovascular drugs

	Binding (%)
Bishydroxycoumarin	99
Warfarin	97
Digitoxin	95
Diphenylhydantoin	93
Trichlormethiazide	92
Diazoxide	91
Ethacrynic acid	90
Clofibrate	90
Hydralazine	87
Quinidine	85

Many cardiovascular drugs are largely bound or stored at inactive sites in tissues which are in equilibrium with the extracellular fluid It seems certain that other drugs can alter the tissue storage of cardiovascular drugs and thereby change their concentration in body fluids and at the site of action Because of methodological difficulties this type of interaction has been little investigated and its clinical importance remains unknown

Interactions affecting biotransformation of cardiovascular drugs Many cardiovascular drugs are lipid soluble nonpolar compounds that must undergo chemical changes which increase their polarity before they can be effectively excreted This biotransformation usually decreases or abolishes pharmacological activity but occasionally both a drug and its metabolite are therapeutically active an inactive precursor drug is converted into an active metabolite or the metabolite may be more toxic than the administered drug [2] Drug biotransformation reactions are most commonly mediated by hepatic microsomal enzymes The activity of enzyme systems in the microsomes can vary manyfold under the influence of genetic environmental and pathologic factors Among the most important is previous or concomitant intake of drugs or foreign chemicals

The ability of many drugs to increase the activity of microsomal enzymes is described as enzyme induction [2, 11] Enzyme inducing drugs

are ubiquitous in clinical practice and the cardiovascular drugs most affected by enzyme induction are the oral anticoagulants [1] and diphenylhydantoin [6] The effects of enzyme induction on cardiovascular drug therapy can be important both when the enzyme inducer is added to therapy and when it is withdrawn In the former case the concentration in the body of the cardiovascular drug whose biotransformation is accelerated may fall below the therapeutic range within a few days and its therapeutic effect may be lost In other patients withdrawal of the inducing drug may cause the concentration of the cardiovascular drug whose metabolic inactivation had been accelerated to climb into the toxic range Either problem can be prevented by appropriate changes in dosage of the cardiovascular drug Since it is difficult to predict the quantitative adjustments required in a given patient, such adjustments must be made on an individual basis

In contrast to enzyme inducing drugs stand drugs which decrease the rate of biotransformation of cardiovascular drugs increase their concentration in the body and enhance their pharmacologic activity [6, 21] Such drugs can slow the metabolic inactivation of cardiovascular drugs either by inhibiting the enzymes responsible for their biotransformation or by competing with the cardiovascular drug for the same enzyme system Many drugs that inhibit the biotransformation of cardiovascular drugs have been identified The cardiovascular drugs most affected by this type of interaction are also the oral anticoagulants [1] and diphenylhydantoin [26] Several fold decreases in their rate of biotransformation and corresponding increases in their concentration in the body have been observed The quantitative aspects in individual patients are again largely unpredictable

Interactions affecting renal excretion of cardiovascular drugs The glomerular filtration of albumin bound cardiovascular drugs is increased when they are partially displaced from albumin by other drugs Some cardiovascular drugs are actively secreted or reabsorbed by tubular transport systems Competition between two drugs for the same transport system is common, but its clinical importance for cardiovascular drugs remains to be shown Filtered or actively secreted lipid soluble cardiovascular drugs are in part passively reabsorbed by the renal tubules during concentration of the tubular fluid An increase in urinary volume by osmotic or natriuretic diuretics can enhance urinary excretion of such drugs Changes in the pH of tubular fluid which increase the ionization and polarity of the cardiovascular drug can have the same effect Urinary flow rate and pH also influence the passive diffusion and pH partitioning into the urine of some cardiovascular drugs The over all urinary excretion of basic drugs (e g procainamide, mecamylamine quinidine and other alkaloids) is increased by acidification and decreased by alkalinization of the urine The reverse is true for acidic drugs Thus the administration of urinary alkalinizing drugs (e g acetazolamide or systemic antacids) or of acidifying drugs (e g ammonium chloride mandelic acid, or sodium citrate) can influence the concentration of cardiovascular drugs in the body [0]

Hemodynamic interactions affecting cardiovascular drugs The distribution of many cardiovascular drugs throughout the body is profoundly influenced by cardiac output and distribution of blood flow [27, 10] Hepatic blood flow importantly affects the rate of biotransformation of some cardiovascular drugs and renal blood flow similarly influences the renal excretion of others All these factors can greatly change the concentration of the cardiovascular drug at its site of action and, therefore, the intensity of its pharmacologic effect To the extent that cardioactive steroids antihypertensive drugs pressor agents, vasodilators antiarrhythmic drugs and diuretics influence cardiac output and the distribution of blood flow they can alter the intensity and duration of action of cardiovascular drugs including their own

Interactions affecting movement of cardiovascular drugs to their site of action Many cardiovascular drugs act at cell surfaces and reach their sites of action by passive diffusion through the extracellular fluid Other drugs must diffuse across cell membranes to reach their intracellular receptors The diffusion into different body compartments of lipid soluble cardiovascular drugs that are weakly acidic or basic is influenced by their state of ionization in these compartments Drugs which alter the intracellular or extracellular pH can change the ratio of intracellular and extracellular concentrations of cardiovascular drugs The pharmacologic effect of this change depends on the location of the drug receptor [0]

Some cardiovascular drugs are carried to their

intracellular site of action by active transport systems When such a system is inhibited by another drug the concentration of the cardiovascular drug at its site of action and the intensity of its pharmacologic effect decrease Such drug interactions are common at adrenergic neurons

Interactions at the site of action of cardiovascular drugs These very common interactions do not involve a change in the concentration of the cardiovascular drug at its site of action (Fig 2) They usually consist of beneficial and planned combinations of the expected therapeutic effects and cannot surprise anybody familiar with the clinical action of the drugs involved In contrast interactions at the site of action involving adverse drug effects are often neglected in therapeutic planning

One type of interaction involving cardiovascular drugs arises from competition for receptor occupancy Such interactions may involve two drugs which activate the same receptors with different effectiveness (agonists) or an active drug and a receptor blocking drug (antagonist) Most antagonists are used therapeutically for the specific purpose of interacting with a cardiovascular drug or an endogenous body substance (e g propranolol with isoproterenol or norepinephrine)

A second type of interaction with cardiovascular drugs at the site of their action results from the effect of one drug on a substance which mediates the action of another Thus by depleting norepinephrine stores in sympathetic nerves reserpine diminishes the action of sympathomimetic amines which act indirectly through release of endogenous norepinephrine (e g amphetamine ephedrine tyramine metaraminol)

The third type of interaction at the site of drug action results from the modification by one drug of tissue response to another The most important example is furnished by the increased myocardial sensitivity to digitalis after potassium depletion by kaliuretic diuretics

The most common interactions between drugs that influence cardiovascular function are additive or subtractive interactions Such interactions are extremely common and quite predictable when they involve the usual therapeutic actions of the drugs Thus all directly and indirectly acting sympathomimetic amines sympathoplegic drugs choline esters cholinesterase inhibitors anticholinergic drugs ganglionic blocking drugs xanthines cardiac glycosides antiarrhythmic agents and many other drugs interact in their effects on heart rate The less specific and basic the drug effect the more subject is it to interaction with other drugs Literally hundreds of drugs interact in their effects on cardiac output arterial pressure or urinary output The action of two drugs may be simply additive (summation) or more than additive (potentiation) Conversely two drugs may oppose each other s action or one may reduce the action of another (inhibition)

Additive drug interactions are often hazardous when they involve unexpected adverse effects of drugs Most unexpected tends to be additive toxicity resulting from not obviously related drug effects For example drug interactions may be responsible for cardiac arrhythmias through the interplay of drug actions as diverse as the kaliuretic effect of thiazides the initial release of endogenous norepinephrine by parenteral reserpine the ability of monoamine oxidase inhibitors to potentiate the action of many catecholamines the hypoxia induced by respiratory depressing doses of narcotics the myocardial ischemia resulting from drug induced hypotension and the effects of cardiac glycosides on myocardial cell membranes

Cardiac glycosides

The therapeutic index of digitalis compounds is one of the smallest of all drugs This is reflected by the high incidence of toxic reactions during the therapeutic use of these drugs which ranged between 10 and 20 per cent in numerous series of hospitalized patients [1,3] Interactions of cardiac glycosides with other drugs contribute significantly to the high prevalence of digitoxicity Some concomitantly administered drugs change the concentration of digitalis at its myocardial site of action others change the sensitivity of the heart to cardiac glycosides

Pharmacokinetic interactions Digoxin the most widely utilized digitalis preparation is usually administered by mouth in tablet form The active drug contained in these tablets is incompletely bioavailable [1,3] The percentage of the active drug absorbed from the gastrointestinal tract is importantly influenced by the formulation of the tablet and by multiple patient and disease factors [1,3,1]

The coadministration of some drugs with digoxin alters the completeness of its absorption These interactions are most important with digoxin tablets that release the active drug

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A second type of interaction with cardiovascular drugs at the site of their action results from the effect of one drug on a substance which mediates the action of another Thus by depleting norepinephrine stores in sympathetic nerves reserpine diminishes the action of sympathomimetic amines which act indirectly through release of endogenous norepinephrine (e g amphetamine ephedrine tyramine metaraminol)

The third type of interaction at the site of drug action results from the modification by one drug of tissue response to another The most important example is furnished by the increased myocardial sensitivity to digitalis after potassium depletion by kaliuretic diuretics

The most common interactions between drugs that influence cardiovascular function are additive or subtractive interactions Such interactions are extremely common and quite predictable when they involve the usual therapeutic actions of the drugs Thus all directly and indirectly acting sympathomimetic amines sympathoplegic drugs choline esters cholinesterase inhibitors anticholinergic drugs ganglionic blocking drugs xanthines cardiac glycosides antiarrhythmic agents and many other drugs interact in their effects on heart rate The less specific and basic the drug effect the more subject is it to interaction with other drugs Literally hundreds of drugs interact in their effects on cardiac output arterial pressure or urinary output The action of two drugs may be simply additive (summation) or more than additive (potentiation) Conversely two drugs may oppose each other s action or one may reduce the action of another (inhibition)

Additive drug interactions are often hazardous when they involve unexpected adverse effects of drugs Most unexpected tends to be additive toxicity resulting from not obviously related drug effects For example drug interactions may be responsible for cardiac arrhythmias through the interplay of drug actions as diverse as the kaliuretic effect of thiazides the initial release of endogenous norepinephrine by parenteral reserpine the ability of monoamine oxidase inhibitors to potentiate the action of many catecholamines the hypoxia induced by respiratory depressing doses of narcotics the myocardial ischemia resulting from drug induced hypotension and the effects of cardiac glycosides on myocardial cell membranes

Cardiac glycosides

The therapeutic index of digitalis compounds is one of the smallest of all drugs This is reflected by the high incidence of toxic reactions during the therapeutic use of these drugs which ranged between 10 and 20 per cent in numerous series of hospitalized patients [31,33] Interactions of cardiac glycosides with other drugs contribute significantly to the high prevalence of digitoxicity Some concomitantly administered drugs change the concentration of digitalis at its myocardial site of action others change the sensitivity of the heart to cardiac glycosides

Pharmacokinetic interactions Digoxin the most widely utilized digitalis preparation is usually administered by mouth in tablet form The active drug contained in these tablets is incompletely bioavailable [4,34,36] The percentage of the active drug absorbed from the gastrointestinal tract is importantly influenced by the formulation of the tablet and by multiple patient and disease factors [34,3]

The coadministration of some drugs with digoxin alters the completeness of its absorption These interactions are most important with digoxin tablets that release the active drug

slowly Any change in bioavailability due to such drug interactions will alter the relationship between the dose of digoxin administered and its concentration throughout the body including at the site of action [34, 35] Drugs that depress gastrointestinal motility increase digoxin bioavailability [34, 35, 36] presumably by allowing dissolved digoxin to remain in longer contact with its absorptive site Cathartics and other drugs that increase gastrointestinal motility can render digoxin absorption less complete [36] Coadministration of drugs such as antacids antidiarrheals charcoal and cholestyramine can decrease digoxin bioavailability through physicochemical interactions with the drug that make it unabsorbable [37, 41] Drugs that affect bioavailability of digoxin should be added to or removed from the therapy of patients chronically treated with digoxin only under careful supervision Monitoring of serum digoxin concentrations can be very helpful when such changes in concomitant therapy are essential [11]

Digoxin is largely eliminated by glomerular filtration and digitoxin is primarily biotransformed in the liver The distribution, renal excretion and hepatic biotransformation of these cardiac glycosides must be influenced by drugs that alter cardiac output or distribution of blood flow but the clinical importance of such changes has not yet been shown Although digitoxin is highly bound to serum albumin and can be partially displaced by other drugs from these binding sites [4] the degree of displacement would be unlikely to influence the therapeutic effectiveness and safety of a given dosage of digitoxin [43]

The hepatic biotransformation of digitoxin to less polar active or inactive metabolites is accelerated during concomitant therapy with phenobarbital [43] diphenylhydantoin [42] and phenylbutazone [12] and probably by some other enzyme inducing drugs The almost twofold reduction in the half life and steady state plasma concentration of digitoxin in man by phenobarbital [43] assures that this interaction is therapeutically important although it has not yet been recognized in the clinical situation Spironolactone another enzyme inducing drug accelerates the biotransformation of digitoxin and decreases its toxicity in animals [44, 45] However therapeutic doses of spironolactone may be weak inducers of digitoxin biotransformation in man [46] and no interaction between the two drugs has been detected clinically

Interactions at site of action The most important drug interactions involving cardiac glycosides are not pharmacokinetic but rather the result of changes in patient sensitivity to these compounds The sensitivity of the myocardium to digitalis is influenced by multiple factors including serum and myocardial potassium calcium, and magnesium concentrations, extracellular and intracellular pH and oxygen tension, adrenergic and cholinergic function, and thyroid status [47, 48] It is obvious that all these factors can be altered by concomitantly administered drugs and that these drugs can therefore interact with cardiac glycosides

Diuretics Perhaps the best known and most dangerous adverse interactions of cardiac glycosides occur with diuretic agents that can induce a negative potassium balance The danger of this type of interaction increases with the degree of potassium depletion In some diuretic treated patients the serum potassium concentration becomes subnormal but considerable reduction in total body potassium may be present even when serum potassium is in the normal range [49, 50] Potassium depletion sensitizes the heart to digitalis compounds and increases the likelihood that a given amount of these drugs in the heart will exert toxic effects usually manifested as dysrhythmias [51, 55] A higher incidence of digitalis toxicity in patients treated with various potassium depleting diuretics has been repeatedly documented in epidemiologic studies [31, 53, 56, 57]

In addition to potassium depletion, most diuretic agents can induce hypomagnesemia [58, 60] and thiazides may cause hypercalcemia [61, 62] Both of these electrolyte disturbances also increase the likelihood of digitalis toxicity, [60, 63] though they are clinically much less important than hypokalemia [54] In all patients treated concurrently with digitalis and diuretics the possibility of imbalances of serum electrolytes should be anticipated the concentration of these ions should be monitored and appropriate preventive or corrective measures must be taken promptly

Other drugs which can induce hypokalemia hypomagnesemia or hypercalcemia can also interact with cardiac glycosides and cause digitoxicity The administration of intravenous calcium salts to patients receiving digitalis compounds requires great caution Chelating agents such as disodium edetate that reduce serum calcium antagonize both the therapeutic and toxic actions of cardiac glycosides [64, 67]

Autonomic drugs Interactions of cardiac glycosides with autonomic drugs are therapeutically important in many clinical situations but their manifestations are complex and difficult to predict in general terms Interaction of sympathomimetic drugs with digitalis compounds can clearly result in cardiac arrhythmias since the two types of drugs share some arrhythmogenic effects on the electrophysiologic properties of the myocardium Indeed it has been suggested that release of endogenous catecholamines is partially responsible for digitoxic arrhythmias The beneficial action of propranolol and certain other beta adrenergic antagonists against digitoxic arrhythmias might fit with this concept but could also reflect the direct membrane stabilizing action of these drugs [3, 8]

Several clinical reports suggest that concurrent administration of cardiac glycosides and rauwolfia alkaloids increases the likelihood of arrhythmias These observations cannot be adequately explained by the release of endogenous catecholamines during the early phase of reserpine therapy nor by the bradycardic effect of chronic reserpine treatment Furthermore in most animal studies reserpine pretreatment actually protected against digitalis induced arrhythmias [70] The evidence is not convincing that interactions of reserpine and cardiac glycosides are of much clinical importance However administration of large parenteral doses of reserpine to patients receiving digitalis compounds is best avoided

Diuretics

Diuretic agents are very commonly used together with other drugs and interact importantly with some of them The interactions of diuretics with cardiac glycosides and with antihypertensive agents are discussed in the sections devoted to these drugs

Interactions among diuretics The commonly used diuretics such as thiazides chlorthalidone and furosemide as well as ethacrynic acid quinethazone mercurials and acetazolamide can cause a negative potassium balance [5, 78] The degree of potassium loss depends on the kaliuretic power of the diuretic the doses and duration of diuretic therapy and multiple patient factors such as potassium and sodium intake mineralocorticoid activity and renal function Potassium depletion can be symptomatic predisposes to digitalis toxicity and may decrease glucose tolerance When chronic it could also cause other as yet unrecognized untoward effects [78] Potassium depletion during the use of the kaliuretic diuretics can be mitigated by their intermittent administration by reductions in their dosage accompanied by decreased sodium intake by increase in dietary potassium intake or by medicinal potassium supplementation Because of physiologic factors and compliance problems none of these maneuvers is universally successful [50, 1, 78, 6]

An alternative and perhaps more effective approach is combination of the potassium wasting diuretic with a potassium sparing drug such as spironolactone or triamterene When the dosages of these two types of diuretics are appropriately adjusted their interaction cannot only maintain potassium balance but potentiate the natriuretic effect In patients at special risk of thiazide induced potassium depletion (digitalis therapy treatment with mineralocorticoids morbid conditions associated with marked secondary hyperaldosteronism) initial therapy with both types of diuretics may be indicated Potassium supplementation should not be used when therapy includes a potassium sparing diuretic [3]

Hypoglycemic drugs Impairment of glucose tolerance during treatment with thiazides and other kaliuretic diuretics occurs to a very variable extent in some diabetic and nondiabetic patients [8] This effect appears to be related in part to potassium depletion since it can be mitigated by potassium supplementation and is not a problem with potassium sparing diuretics such as spironolactone or triamterene However effects of diuretics on insulin secretion or action [87] may also play a role Some diabetic patients treated with oral hypoglycemic agents or with insulin may require an increase in the dosage of these agents or a change to a more potent drug when kaliuretic diuretics are added to therapy Fortunately this is necessary in only about 10 per cent of such patients and in even fewer when a negative potassium balance is prevented by appropriate measures The interaction between diuretics and hypoglycemic drugs is a minor and easily managed problem

Antihyperuricemic agents Thiazides and most other diuretics decrease renal excretion of uric acid and raise its serum concentration in normouricemic and hyperuricemic subjects In hyperuricemic patients treated with allopurinol or uricosuric drugs (probenecid sulfinpyrazone) they interfere with the hypouricemic action of these drugs This undesirable interaction can be

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managed by an increase in the dose of the antihyperuricemic drug[14, 88, 89] or by substitution of a diuretic such as spironolactone which does not affect uric acid metabolism

Aminoglycoside antibiotics The dose related ototoxic potential of aminoglycoside antibiotics (kanamycin, gentamycin streptomycin and neomycin) is well established Ethacrynic acid and to a much lesser extent furosemide can also cause transient or permanent hearing loss particularly when administered intravenously in high doses or to patients with impaired renal function The combined use of these diuretics and of aminoglycoside antibiotics results in additive ototoxicity and should be avoided particularly in the presence of significant azotemia[90, 93]

Adrenergic drugs

Sympathomimetic agents are widely used in cardiovascular therapy because of their important effects on the electrical and mechanical behavior of the heart and on the caliber of resistance and capacitance vessels They frequently interact with other drugs and such interactions can result either in loss of therapeutic effectiveness or in serious toxic effects

In order to consider interactions of other drugs with sympathomimetics these drugs must be classified in two ways The first relates to their relative activity at the alpha and beta adrenergic receptor sites Isoproterenol is a beta adrenergic stimulator and therefore causes cardiac excitation and peripheral vascular relaxation Methoxamine is primarily an alpha receptor stimulator has little cardiac action and constricts peripheral vascular beds Most sympathomimetic amines, including norepinephrine, epinephrine and dopamine, are both alpha and beta receptor agonists, but their ratio of activity at the two types of receptors varies greatly

The second classification of sympathomimetic amines is based on whether the drug stimulates adrenergic receptors directly (e g, epinephrine norepinephrine, isoproterenol phenylephrine methoxamine) or acts indirectly by releasing norepinephrine from adrenergic neurons (e g, amphetamine, methamphetamine, mephentermine, tyramine)[94] Some sympathomimetics such as ephedrine metaraminol, and phenylpropanolamine possess both direct and indirect activity (mixed action)

Adrenergic receptor antagonists Propranolol and many other beta adrenergic receptor blocking drugs competitively antagonize the actions of directly or indirectly acting sympathomimetics on all beta receptors[95] Recently cardioselective antagonists have been developed (e g practolol) which block primarily cardiac beta receptors (β_1) Other beta blockers (e g butoxamine) are more specific for peripheral vascular and bronchial beta receptors (β_2) The action of sympathomimetic amines on alpha receptors is antagonized by alpha adrenergic blocking drugs such as phentolamine and phenoxybenzamine Since deliberate use is made for therapeutic purposes of these highly specific interactions between adrenergic agonists and antagonists, they should not cause clinical problems

Reserpine Reserpine and other rauwolfia alkaloids decrease the storage of norepinephrine in sympathetic nerve endings[9] Thus it would be expected that these drugs decrease the action of sympathomimetic amines with indirect or mixed action This effect has been clearly demonstrated in experimental animals but clinical data are not convincing[97, 101] Most probably the interaction fails to assume clinical importance in most patients because the depletion of releasable norepinephrine stores by therapeutic doses of reserpine is not profound However if sympathomimetic stimulation is desirable in a patient on chronic reserpine therapy it would be best to use one of the direct acting adrenergic drugs[101] Smaller than usual doses of these drugs may be effective because reserpine treated patients tend to be hypersensitive to direct acting sympathomimetics

Guanethidine Chronic administration of this drug leads to progressive depletion of norepinephrine stores in sympathetic nerve endings[96] Accordingly the release of norepinephrine by indirect acting sympathomimetic drugs is diminished in guanethidine treated patients However there is also supersensitivity of the effector cells to norepinephrine presumably because norepinephrine reuptake into the neuron is decreased by guanethidine[10, 103] As a consequence, the over all effect of guanethidine therapy on the response to indirectly acting sympathomimetic amines appears to be variable In contrast the action of sympathomimetic amines which directly stimulate adrenergic receptors is always increased during guanethidine therapy Norepinephrine epinephrine, or other directly acting adrenergic

agents must be used with caution in guanethidine treated patients One should remember that such agents are often contained in unsuspected products such as topical decongestants and nonprescription antitussive antiasthmatic and antiobesity preparations

Monoamine oxidase inhibitors The enzyme monoamine oxidase (MAO) is involved in the oxidative deamination of norepinephrine in sympathetic nerve endings Drugs which inhibit the action of this enzyme (e g pargyline phenelzine nialamide isocarboxazid tranylcypromine furazolidone) cause the concentration of norepinephrine in the nerve endings to rise This leads to a greater release of norepinephrine when indirectly acting sympathomimetic compounds (amphetamines ephedrine tyramine) are administered Tyramine is contained in many foods including certain cheeses chicken liver pickled herring yeast red wines and beer but is normally largely metabolized by MAO in the intestines and liver During administration of MAO inhibitors a greater fraction of ingested tyramine reaches the systemic circulation and thus further contributes to the exaggerated release of norepinephrine Sympathomimetic amine precursors such as levodopa can also release exaggerated amounts of norepinephrine or dopamine in MAO inhibitor treated patients [0]

Ingestion of tyramine containing foods[109 5] or administration of indirectly acting sympathomimetic amines [15 1 0] or levodopa [05 1] has led to serious hypertensive crises and fatalities in patients treated with MAO inhibitors [22 1] The clinical picture of palpitation hypertension severe headaches and intracranial bleeding is due to excessive norepinephrine release The treatment of choice is intravenous infusion of alpha adrenergic receptor blocking drugs such as phentolamine Patients treated with MAO inhibitors must receive dietary advice [26] Indirectly acting sympathomimetic amines (which are common components of over the counter cold remedies) or levodopa should not be taken by such patients

Anesthetic agents The occurrence of serious cardiac dysrhythmias due to interaction between adrenergic agents and general anesthetics has long been recognized and recently reviewed in detail [9] The exact mechanism of the interaction remains unclear [1] but the anesthetics markedly reduce the dose of sympathomimetics required to induce arrhythmias The interaction involves primarily beta adrenergic receptor stimulating drugs and can be prevented or treated with beta receptor blocking drugs [31] Epinephrine and norepinephrine have been most frequently incriminated [2 13 133] but isoproterenol [12 131] metaraminol [1] and other drugs resulting in beta adrenergic stimulation[12 134] have also been involved More rarely alpha receptor stimulants such as methoxamine and phenylephrine have precipitated arrhythmias during anesthesia [129 134] perhaps because their pressor action can exert arrhythmogenic effects [131] Intravenous administration of adrenergic drugs is most likely to lead to this interaction but arrhythmias may even follow their intramuscular or subcutaneous injection

Arrhythmias have been attributed to interaction of adrenergic drugs with many anesthetic agents Cyclopropane may pose the greatest risk and halogenated hydrocarbon anesthetics (chloroform ethyl chloride trichloroethylene halothane and perhaps to a lesser extent fluroxene and methoxyflurane) have also been implicated [2 12 3 137] Nitrous oxide and ether cause little if any sensitization of the myocardium to adrenergic agents

This potentially lethal interaction should be avoided by selecting non interacting anesthetics when surgical use of epinephrine will be necessary Other need for adrenergic therapy during the use of interacting anesthetics can be minimized by careful induction and prevention of hypoxia hypercapnia or acidosis When administration of adrenergic agents becomes essential the drugs should be administered subcutaneously slowly and in a low dose When only a peripheral vasoconstrictor effect is required phenylephrine or methoxamine are the sympathomimetic drugs of choice

Other drugs Interactions of adrenergic agents with phenothiazines (decreased pressor effect of indirectly acting sympathomimetics) [13] and with tricyclic antidepressants (potentiation of pressor effects and hypertensive crises) have been reported but their clinical importance appears minor

Antihypertensive drugs

No other form of cardiovascular therapy offers as many examples of useful drug interactions as the treatment of hypertension [0] Diuretic drugs

are now almost universally added to other anti hypertensive agents in order to allow the use of the latter in smaller doses and to prevent sodium retention extracellular and intravascular volume expansion and the development of refractoriness to therapy[140,14] Recently it has been demonstrated that the combination of propranolol or other beta adrenergic receptor antagonists with hydralazine or other direct acting vasodilator drugs is extremely effective in the treatment of hypertension[4,14] Propranolol can prevent the tachycardia, increased cardiac output and hyper reninemia caused by vasodilators and thereby potentiate their antihypertensive action[4] The advantages of treating all but the mildest cases of hypertension with more than one drug are now fully accepted[140,143]

On the other hand, antihypertensive drugs can be involved in unexpected and adverse interactions with drugs not used in the therapy of hypertension The effects of some antihypertensives on the action of adrenergic drugs have already been discussed

Guanethidine Guanethidine is selectively concentrated in adrenergic nerve endings by an active transport mechanism (norepinephrine pump ')[8,144,146] This transport mechanism is inhibited by the tricyclic antidepressant drugs, imipramine desipramine amitriptyline, nortriptyline and protriptyline[147,150] and to a lesser extent by doxepin[151] This inhibition decreases or prevents the hypotensive effect of guanethidine[147,143] The decrease of the hypotensive action requires about two days for full development and guanethidine s action is not fully restored in less than one week after cessation of antidepressant therapy[145,149,15] The interaction between guanethidine and tricyclic antidepressants exposes hypertensive patients to loss of blood pressure control when one of the latter drugs is added to guanethidine therapy Even more dangerous is the excessive postural hypotension which can develop when blood pressure has been controlled with guanethidine in patients treated with a tricyclic antidepressant and the latter drug is then withdrawn Chlorpromazine, and probably other phenothiazines, similarly interfere with the action of guanethidine[153]

Amphetamine, dextroamphetamine, methamphetamine, ephedrine and methylphenidate also antagonize the antihypertensive action of guanethidine[145,154] This interaction may be explained by competition with guanethidine for the norepinephrine pump and/or for storage in the sympathetic nerve ending[145,154,156] The clinical results of the interaction between guanethidine and these drugs are similar to those described for guanethidine and the tricyclic antidepressants Coadministration of guanethidine with any of these drugs is best avoided by choosing another antihypertensive when their administration is essential

Monoamine oxidase inhibitors Pargyline is a monoamine oxidase (MAO)-inhibiting drug which is used in the treatment of hypertension The MAO inhibitors interact with a host of other drugs, and these interactions can be life threatening or lethal[157] The serious interactions between MAO inhibitors and indirectly acting sympathomimetics and tyramine containing foods have been discussed previously In some patients the effects of sedatives, hypnotics and narcotic analgesic drugs are potentiated by MAO inhibitors[158,163] These drugs may also intensify the central nervous system depression produced by ethyl alcohol and the hypoglycemic action of insulin[164,165] There have been reports of severe interactions of MAO inhibitors with tricyclic antidepressants taking the form of excitement, delirium, hyperpyrexia, tremors convulsions coma, and death[166,169] This interaction is not well documented its mechanism is not clear[16] and it occurs only in occasional patients[170,17]

Some of the above drug interactions with MAO inhibitors probably reflect their nonspecific inhibition of drug metabolizing enzymes[13,173,174] and the same mechanism could potentiate the action of many other biotransformed drugs In view of the multiple and often serious drug interactions and of their limited antihypertensive effectiveness the MAO inhibitors are not to be recommended for the therapy of hypertension

Antiarrhythmic agents

The concomitant use of other drugs is very common during antiarrhythmic therapy Indeed it has become widespread practice to combine several antiarrhythmic drugs (lidocaine diphenylhydantoin, quinidine procainamide propranolol) when attempting to correct or prevent the more serious and refractory arrhythmias Implicit in this approach are the assumptions that the therapeutic actions of the various antiarrhythmic drugs are additive and that their adverse effects

are not Both these assumptions are frequently incorrect

While all commonly used antiarrhythmic drugs directly decrease the rate of diastolic depolarization of cardiac fibers capable of impulse formation their effects on conduction velocity and on the refractory period in various parts of the heart differ both quantitatively and qualitatively[55 75 78] Sympathetic and vagal stimulation of specific parts of the heart are also very differently affected For these reasons the administration of a second antiarrhythmic drug to a patient already receiving one such drug with less than satisfactory results does not necessarily produce an additional effect toward correcting or preventing the arrhythmia The new drug may counteract the electrophysiologic effect of the first that is most crucial for control of the particular arrhythmia At the same time the important toxic effects (depression of myocardial contractility peripheral vasodilation hypotension) may be fully additive[7 60] Thus it would have been preferable to increase the dose of the first drug rather than to add a second The difficulty in predicting clinically the result of interactions between antiarrhythmic drugs is not surprising since in a given patient we seldom know the precise electrophysiologic effect required to control the arrhythmia nor the exact action that will be exerted by a given concentration of any antiarrhythmic drug in that patient s abnormal myocardium

Therapeutic interactions between antiarrhythmic drugs in the treatment of life threatening arrhythmias must be carefully planned on theoretical grounds To combine drugs with essentially identical actions such as quinidine and procainamide tends only to confuse the clinical picture On the other hand interactions of the effects of one of these drugs with lidocaine diphenylhydantoin or propranolol may at times be more effective than any single drug even in the maximum tolerated dose[1 9] However whether the net effect of using more than one drug is more beneficial than harmful must be continuously re evaluated by close observation of the patient In these complex and serious therapeutic situations knowledge of the plasma concentrations of the individual drugs can add much to the success of therapy[76]

Lidocaine Lidocaine is cleared from the body by rapid inactivation in the liver The concentration of lidocaine in serum and at its myocardial site of action and consequently the intensity of the antiarrhythmic activity of a given dose or infusion rate rise with decreases in cardiac output and hepatic blood flow[27 29 30] The volume of distribution of the drug is decreased in congestive heart failure and its rate of clearance by hepatic biotransformation is reduced when hepatic blood flow falls or in the presence of liver disease[30] Drugs that raise (isoproterenol)[190] or lower hepatic blood flow (propranolol[81] norepinephrine[19]) proportionately change body clearance of lidocaine and inversely affect serum lidocaine levels Similar interactions are sure to occur between lidocaine and other hemodynamically active drugs and illustrate the importance for pharmacokinetic drug interactions of changes in cardiac output and perfusion of drug metabolizing organs

Diphenylhydantoin This drug is primarily inactivated in the liver and is involved in a host of pharmacokinetic interactions with other drugs[26] Its hepatic biotransformation can be accelerated by barbiturates and other enzyme inducing drugs[1 95] resulting in a lower concentration of diphenylhydantoin in the body and in decreased action of any given dosage Inhibition of diphenylhydantoin biotransformation can be caused by coadministration of drugs such aminosalicylate bishydroxycoumarin chloramphenicol disulfiram isoniazid methylphenidate phenylbutazone and others[9 19] All these drugs therefore potentiate the antiarrhythmic action of chronically administered diphenylhydantoin

These interactions are not clinically important during the usual short term antiarrhythmic use of diphenylhydantoin In the rare patient who receives diphenylhydantoin for chronic antiarrhythmic prophylaxis they definitely contribute to the unpredictability of the relationship between dosage and serum concentration of diphenylhydantoin In such patients the serum concentration of diphenylhydantoin should be periodically determined and kept between 10 and 20 mg per liter by appropriate dosage adjustments[6 40]

Quinidine Because of its propensity to cause gastrointestinal symptoms quinidine is commonly administered with antacids Such compounds may delay the absorption of quinidine but are unlikely to render it incomplete Thus the interaction is unimportant during chronic quinidine

therapy and no clinical effects have been detected

Drugs that increase or decrease urinary pH have corresponding effects on the serum concentration of quinidine [91] However, this interaction is less important than in the case of procainamide because renal excretion of the unchanged drug accounts for a smaller fraction of the elimination of quinidine [2,3]

Quinidine can enhance the neuromuscular blocking effects and ventilatory depression of patients treated with tubocurarine, succinylcholine and decamethonium [93,3] Postoperative patients who have apparently recovered from such muscle relaxing drugs may require renewed ventilatory support when given quinidine particularly by the parenteral route

Procainamide The serum concentration and antiarrhythmic activity of a given dosage or infusion rate of procainamide must also be influenced by drugs which alter cardiac output and renal blood flow,[28, 9, 96] but this has not yet been clinically demonstrated Since procainamide is a weak base and excreted largely in unchanged form by the kidneys its half life in the body is considerably prolonged when the urinary pH increases [2] Thus drugs such as sodium bicarbonate or acetazolamide potentiate the action of procainamide whereas acidification of the urine by other drugs reduces it

Propranolol The previously discussed interaction of propranolol and other beta adrenergic blocking drugs with norepinephrine epinephrine isoproterenol, or any other beta adrenergic agonist is highly specific and therapeutically useful Occasionally it may be undesirable as when a propranolol treated patient requires sympathomimetic bronchodilator therapy [0, 2]

In rare patients propranolol may interact with insulin and oral hypoglycemic agents by interfering with the glycogenolytic effect of catecholamines normally released in response to hypoglycemia produced by excessive dosage of these drugs [2, 9, 14] The usual warning signs of such hypoglycemic episodes such as nervousness tachycardia and diaphoresis may also be suppressed [2,11]

Anticoagulant drugs

Among all widely used drugs the coumarin anticoagulants (warfarin sodium bishydroxycoumarin, ethylbiscoumacetate acenocoumarol phenprocoumon) are the most susceptible to therapeutically important drug interactions First many patients take oral anticoagulants over long periods of time and almost always receive one or more other drugs concurrently Second, the pharmacokinetic fate and the pharmacologic action of coumarins in the body are complex and are altered by many drugs Third, the exact intensity of the pharmacologic action of coumarin anticoagulants is quite important during their therapeutic use, and relatively small decreases or increases in the intensity of their action can lead to therapeutic failures or hemorrhagic reactions The important therapeutic problem of drug interactions involving coumarin anticoagulants has recently been reviewed in detail [1] Although the oral anticoagulants, particularly bishydroxycoumarin can alter the metabolic fate and pharmacologic effects of some drugs [1] the modification of coumarin action by other drugs is clinically far more important

Mechanisms of drug interactions with oral anticoagulants Drugs can modify the anticoagulant action of coumarins by a variety of mechanisms (Fig 3) They can alter the concentration of the coumarin antagonist vitamin K at the hepatic site of synthesis of factors II, VII, IX and X Other drugs can change the absorption of coumarins from the gastrointestinal tract their binding to serum albumin, or their biotransformation in the liver to inactive compounds Still other drugs interact with coumarin anticoagulants by exerting a direct effect on the synthesis or catabolism of the prothrombin complex Finally some drugs interact with the anticoagulant action of the coumarins by affecting nonprothrombin complex-dependent hemostatic mechanisms such as platelet function or vascular integrity The interactions of many drugs with coumarins gain in complexity by involving more than one mechanism

Interactions involving vitamin K In subjects who are being treated with coumarin anticoagulants the prothrombin complex content of plasma is determined by the opposing effects of the coumarin and of vitamin K on its hepatic synthesis During coumarin therapy any change in the availability of vitamin K to the liver will alter the plasma concentration of the vitamin K-dependent clotting proteins but little is known about the fate of vitamin K after absorption The absorption of dietary vitamin K should be decreased by drugs that bind bile salts increase

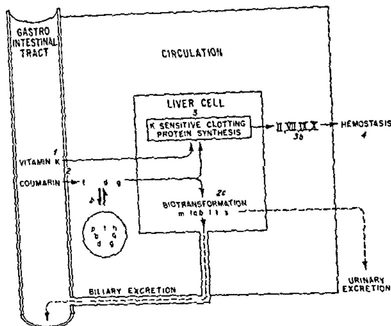


Fig 3 Sites of drug interactions with the anticoagulant action of coumarins 1 Vitamin K bioavailability 2a coumarin absorption 2b coumarin binding to serum albumin 2c coumarin biotransformation 3a prothrombin complex synthesis 3b prothrombin-complex catabolism 4 hemostasis

intestinal motility or interfere with mucosal function but no such drug has been convincingly shown to potentiate the hypoprothrombinemic action of coumarins Similarly antibiotic induced reduction in synthesis of vitamin K by intestinal bacteria has little influence on prothrombin complex synthesis in anticoagulated patients unless their dietary intake is grossly deficient [1]

Interactions involving coumarin metabolism The ability of other drugs to alter the fate of coumarins in the human body is responsible for the most important drug interactions with coumarins Any drug induced change in the absorption distribution or disposition of a coumarin alters its hypoprothrombinemic effect The pharmacokinetics of individual coumarins in man are similar but not identical Most importantly bishydroxycoumarin is more slowly and incompletely absorbed from the gastrointestinal tract and ethylbiscoumacetate is less bound to serum albumin than other coumarins Thus drug effects on absorption are most important with bishydroxycoumarin and drug interactions related to serum albumin binding are least important with ethylbiscoumacetate

Drugs that can decrease the rate or completeness of gastrointestinal absorption of bishydroxycoumarin and at times of other coumarins include compounds that increase gastric pH (e g antacids) alter gastrointestinal motility (e g laxatives anticholinergics) interfere with normal mucosal function (e g neomycin colchicine) form complexes with coumarins (e g cholestyramine) or are nonabsorbable materials that dissolve or adsorb coumarins (e g mineral oil charcoal) However these interactions have not been clinically important perhaps because the same drugs interfere with the absorption of vitamin K and therefore cause little net change in prothrombin complex synthesis

Many drugs decrease the binding of coumarins to serum albumin The displacing drugs are generally acidic compounds that are highly protein bound administered in large doses and accumulate to high levels in plasma Since 97 and 99 per cent of therapeutic serum concentrations of warfarin and bishydroxycoumarin are bound to serum albumin displacement of even a small amount of these drugs from albumin causes a large increase in the concentration of the drug in serum This can result in a manifold increase in the hypoprothrombinemic effect of a given dosage of the anticoagulant Administration of strongly displacing drugs to patients chronically treated with coumarins commonly causes severe hypoprothrombinemia and bleeding and has

resulted in many fatalities [11] The potentiation of the hypoprothrombinemic action of coumarins by displacing drugs is always transient even when the interacting drug is continued, because an increase in the concentration of free coumarin in the serum accelerates coumarin biotransformation [2, 21] The time course of onset and subsidence of the potentiation is complex and depends on the biological half life of the individual coumarin and displacing drug [11, 21]

The coumarins are inactivated primarily through hydroxylation by hepatic microsomal mixed function oxidase enzymes [1] Any drug that increases or decreases the activity of these enzymes can inhibit or enhance the hypoprothrombinemic action of the coumarins Many drugs which increase the activity of the coumarin metabolizing hepatic enzymes have been identified [21, 24, 25, 1] In any given subject, the increase in the rate of coumarin metabolism, the decrease in the coumarin serum concentration, and the inhibition of the hypoprothrombinemic effect of the anticoagulant are fairly reproducible [11, 222] However, the degree of inducibility varies considerably among individuals and is in part genetically determined [3] The extent to which coumarin metabolizing enzymes are induced in man also depends on the specific inducing drug its dosage, and the duration of exposure A single therapeutic dose of a potent inducer can accelerate coumarin metabolism appreciably [224] but up to one week of exposure to some inducing agents may be required for maximum enzyme induction [21] Upon withdrawal of the inducing drug the return of the rate of coumarin metabolism to its original level requires several weeks [225, 26] The most important clinical consequence of the induction of coumarin metabolizing enzymes occurs in patients whose prothrombin time has been well controlled during the administration of an enzyme inducing drug When the inducing drug is discontinued, such patients will gradually develop excessive hypoprothrombinemia and may bleed

The opposite problems are encountered with drugs that decrease the rate of biotransformation of coumarins and increase their serum concentration [27, 228] Because such drugs potentiate the hypoprothrombinemic action of coumarins, the maintenance dose of the anticoagulant must be reduced when they are added to therapy and increased when they are withdrawn

Interactions involving direct effects of other drugs on prothrombin-complex concentration Drugs that change the concentration of vitamin K-dependent clotting factors in plasma by directly altering their synthesis or catabolism also interact with coumarin anticoagulants They may cause major changes in the prothrombin time of anticoagulated patients, though they do not appreciably alter it in normal subjects Some such drugs depress clotting factor synthesis by specifically antagonizing the action of vitamin K as do the coumarins [9, 211] Less specifically all drugs that are inhibitors of protein synthesis [3] or impair hepatic function [33] can decrease the rate of prothrombin complex synthesis in anticoagulated subjects and potentiate their hypoprothrombinemia [33] Thyroid hormones and other drugs that produce hypermetabolic states increase the rate of catabolism of the vitamin K-depending clotting factors[234] and thereby increase coumarin induced hypoprothrombinemia

Interactions involving effects of other drugs on hemostasis Normal hemostasis requires the unimpaired functioning of many intravascular and extravascular mechanisms in addition to those depending on the activity of vitamin K sensitive clotting proteins Any of the many drugs that interfere with the normal function of parts of the hemostatic process unrelated to prothrombin complex activity[235, 246] may interact with both the desired therapeutic and the hemorrhagic complications of coumarin therapy Drug effects on platelet function and ulcerogenic actions of drugs are the best studied examples Such drugs can cause serious bleeding in coumarin treated patients even when their prothrombin time remains in the desired therapeutic range

Interactions of individual drugs with coumarins During the past 15 years many drugs have been suspected of interacting with coumarin anticoagulants Such suspicions have often been based on speculative interpretations of a single clinical event Reports of uncontrolled clinical impressions are useful leads but must be followed up by controlled investigations It is unfortunate that some drugs have gained the false reputation of interacting with coumarins on the basis of a single anecdotal report The clinical and experimental evidence relating to the interaction of individual drugs with coumarins has recently been analyzed and referenced [21] Since then further reports have supported the effects on coumarin metabolism or hypoprothrombinemic

Table V Inhibition of the hypoprothrombinemic action of coumarins

Drug	*Mechanism*
Barbiturates	Acceleration of coumarin metabolism
Carbamazepine	Acceleration of coumarin metabolism
Cholestyramine	Inhibition of coumarin absorption
Diphenylhydantoin	Acceleration of coumarin metabolism
Ethchlorvynol	Acceleration of coumarin metabolism?
Glutethimide	Acceleration of coumarin metabolism
Griseofulvin	Inhibition of coumarin absorption? Acceleration of coumarin metabolism?
Oral contraceptives	Increase of clotting factor synthesis
Rifampin	Acceleration of coumarin metabolism?
Vitamin K	Increase of clotting factor synthesis

action of anabolic steroids[2,7,2,9] antacids[215,21] carbamazepine [0] chloral hydrate[2,1,3,3] cholestyramine [5] clofibrate[2] diphenylhydantoin[24,245] disulfiram[2] ethacrynic acid[2] nalidixic acid [7] rifampin [3] tolbutamide[2,5] and triclofos[2] Others have documented the absence of clinically significant interactions of important drugs with coumarins [3]

The number of drugs clearly shown to inhibit the hypoprothrombinemic action of coumarins in man in a therapeutically important fashion is relatively small (Table V) All seem to act by inhibiting gastrointestinal absorption of coumarins by accelerating their hepatic metabolism through enzyme induction or by directly increasing clotting factor synthesis It is impossible to predict the amount of change in the relation of anticoagulant dosage to prothrombin prolongation which will occur when intake of these drugs is started changed or stopped in a patient treated with coumarin anticoagulants Chronic administration of inhibiting drugs can decrease plasma half life and plasma concentration of the coumarin by 50 per cent or more and may require at least a doubling of the anticoagulant dosage to maintain the same hypoprothrombinemic effect However one cannot rely on this relation in any given patient Frequent measurement of prothrombin times and appropriate adjustment of anticoagulant dose are essential when inhibiting drugs must be used in patients receiving a coumarin Even with careful monitoring optimal control of hypoprothrombinemia may be difficult in a patient receiving such drugs and it is best to avoid them altogether [2,3]

A large number of drugs have been found to cause clinically important potentiation of the

Table VI Enhancement of the hypoprothrombinemic action of coumarins

Drug	*Mechanism*
Allopurinol	Inhibition of coumarin metabolism
Anabolic steroids	Decrease in circulating vitamin K? Direct depression of clotting factor synthesis? Increase in clotting factor catabolism?
Chloral hydrate	Decrease in coumarin albumin binding
Chloramphenicol	Inhibition of coumarin metabolism
Clofibrate	Decrease in circulating vitamin K? Decrease in coumarin albumin binding? Inhibition of coumarin metabolism?
Dextrothyroxine	Decrease in circulating vitamin K? Increase in clotting factor catabolism?
Diazoxide	Decrease in coumarin albumin binding
Disulfiram	Inhibition of coumarin metabolism
Ethacrynic acid	Decrease in coumarin albumin binding
Glucagon	Decrease in clotting factor synthesis?
Nalidixic acid	Decrease in coumarin albumin binding
Neomycin	Decrease in vitamin K absorption?
Nortriptyline	Inhibition of coumarin metabolism
Phenylbutazone	Decrease in coumarin albumin binding
Quinidine	Direct depression of clotting factor synthesis?
Salicylate	Direct depression of clotting factor synthesis?
Sulfonamides long acting	Decrease in coumarin albumin binding
Thyroid drugs	Increase in clotting factor catabolism
Tolbutamide	Decrease in coumarin albumin binding
Triclofos	Decrease in coumarin albumin binding

hypoprothrombinemic action of coumarins (Table VI) This enhancement has a number of different mechanisms the most important being displacement of warfarin from binding sites on serum albumin inhibition of warfarin metabolism and direct depression of clotting factor synthesis Both the time course and the degree of potentiation of the hypoprothrombinemic actions of coumarins vary with the mechanism of the interaction with the specific drug and with its dose Twofold or threefold enhancement of coumarin action within a few days occurs with usual doses of some potentiating drugs[211] However the time course and extent of interaction vary considerably among patients and the only safe course when potentiating drugs are added to or withdrawn from therapy is to monitor

Table VII Therapeutic alternatives for coumarin treated patients

Interacting drug	Substitute
Barbiturates	Flurazepam
Chloral hydrate	Flurazepam
Ethchlorvynol	Flurazepam
Glutethimide	Flurazepam
Triclofos	Flurazepam
Chloramphenicol	Appropriate antibiotic
Long acting sulfonamides	Appropriate antibiotic
Nalidixic acid	Appropriate antibiotic
Allopurinol	*Probenecid*
Tolbutamide	Chlorpropamide
Phenylbutazone	Indomethacin
Salicylate	Acetaminophen Indomethacin
Quinidine	Procainamide
Diazoxide	Nitroprusside

the prothrombin time closely and to adjust coumarin dose according to the results obtained

Prevention of untoward events due to anticoagulant interactions A few simple precautions can prevent most adverse clinical events due to drug interactions with coumarins

1 When first prescribing an oral anticoagulant the physician should know all other drugs the patient is taking and caution him not to change his intake of either prescription or nonprescription drugs without first communicating with the physician

2 For patients chronically treated with oral anticoagulants some strongly interacting drugs should be avoided and therapeutic alternatives utilized instead (Table VII)

3 Changes of drug therapy in patients taking a coumarin should be kept to the minimum possible When necessary changes involve known interacting drugs some anticipatory alteration in coumarin dosage may be made but close monitoring of prothrombin time for some weeks after the change and appropriate adjustment of coumarin dosage on that basis is most important Drugs not yet shown not to interact with coumarins are best regarded with suspicion and used only with the same precautions

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Appraisal and reappraisal of cardiac therapy

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Electrophysiology and pharmacology of cardiac arrhythmias VII Cardiac effects of quinidine and procaine amide B

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Effects on electrical activity of cardiac cells

Quinidine and procaine amide have quite similar effects on the transmembrane potentials and electrical activity of cells from all parts of the mammalian heart Most of these effects are exerted directly by the drugs but some are due to drug induced modification of responses to autonomic mediators For the most part drug effects have been described for normal cardiac cells and only recently has systematic investigation of drug actions on depressed or diseased fibers been initiated The information resulting from these latter studies will be essential for a correct understanding of relationships between drug effects and antiarrhythmic activity Because of their greater suitability for study by intracellular microelectrodes cardiac Purkinje fibers have been used for the majority of investigations

A Effects on threshold and action potential upstroke Quinidine and procaine amide like other drugs exerting a local anesthetic action depress the responsiveness of cardiac cells [7,1] Both drugs in a dose dependent manner decrease the maximum rate of depolarization and the amplitude of the action potential upstroke recorded from atrial and ventricular muscle fiber and Purkinje fibers (Fig 3) This effect is seen at concentrations which do not decrease the resting potential or maximum diastolic potential i e 30 μg/ml in Tyrode solution or 5 to 10 μg/ml in blood [9,20] The decrease in responsiveness thus appears to result from a direct effect on the mechanism controlling the voltage and time dependent increase in a sodium conductance [17,21] Most investigators have found that for a given concentration of drug the decrease in responsiveness is increased by elevating extracellular potassium concentration ([K]) and diminished by lowering [K] [22,3]

Conduction velocity and excitability are modified by those effects of quinidine and procaine amide on the mechanism responsible for generating the active response Because there is less of an increase in the inward depolarizing current for any degree of depolarization the threshold potential is shifted to less negative values [17] As a result more stimulus current is needed to initiate an active response from the normal level of resting potential Because of the effects on active response and threshold potential conduction velocity usually is decreased progressively as drug concentration rises There is one exception to this statement If conduction is measured in Purkinje fibers which demonstrate marked Phase 4 depolarization low concentrations of either quinidine or procaine amide may increase the speed of impulse propagation [2,25] This occurs for the following reason In the presence of marked phase 4 depolarization the action potential upstroke is initiated at quite a low level of membrane potential Consequently upstroke velocity and amplitude are low and the impulse propagates slowly Low concentrations of drug will markedly decrease the slope of phase 4 and permit the

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mechanism during repolarization The increase in action potential duration is more prominent at low rates and is counteracted in large measure by the actions of catecholamines and sympathomimetic agents

C Effects on resting potential maximum diastolic potential and automaticity Both quinidine and procaine amide decrease the slope of the Phase 4 depolarization which is associated with normal automaticity This effect is demonstrated most clearly for cardiac Purkinje fibers but in sufficient concentration each drug will decrease Phase 4 depolarization in atrial specialized fibers and in cells of the sinoatrial node At low concentrations of drug the decrease in rate of automatic firing results primarily from the effect on the slope of phase 4 depolarization at higher concentrations the shift in threshold potential towards zero contributes to the slowing because threshold potential has been moved farther from maximum diastolic potential [7] Quite high concentrations of quinidine and procaine amide will decrease the resting potential and maximum diastolic potential of normal fibers this effect is noted at lower drug concentrations if the fibers are diseased or depressed

Although the usual effect of these antiarrhythmic drugs is to decrease the slope of phase 4 depolarization and the rate of automatic firing in high concentrations quinidine and to a lesser extent procaine amide will increase the slope of phase 4 depolarization and spontaneous rate This effect is demonstrated only when there has been some drug induced decrease in maximum diastolic potential

There is increasing evidence that in partially depolarized cardiac fibers the action potential results from an abnormal mechanism—an inward current carried in large part by calcium rather than sodium and through *slow* rather than through the normal *fast* channels [28] In such fibers phase 4 depolarization may be present and may result in automatic firing The effects of quinidine and procaine amide on the type of phase 4 depolarization recorded from partially depolarized fibers have not yet been described completely Nevertheless some information is available concerning human atrial tissues In these studies markedly depolarized fibers with spontaneous rhythm were less responsive to procaine amide than they were to the calcium blocker verapamil

Ionic mechanisms for actions on cardiac transmembrane potentials It seems most likely that the major actions of procaine amide and quinidine on the electrical activity of cardiac cells are the result of drug induced changes in the conductance of the cell membrane to several species of ions The best information on this subject is derived from studies on the effects of procaine and other local anesthetics on the excitable membrane of squid giant axons[29,3] unfortunately many of the studies on cardiac fibers which are needed to provide direct evidence for comparability between nerve and heart still are lacking In general it seems clear that local anesthetics like procaine and procaine amide penetrate the cell membrane in the uncharged form and then as a charged particle, interact with a site on the inner surface of the membrane which exerts control over the fast sodium channel As a result the sodium conductance of the membrane increases less and sometimes less rapidly when the membrane is depolarized This depression of the voltage and time dependent increase in sodium conductance results in a decrease in the rate of change of membrane potential during phase 0 (a decrease in V_m) and a decrease in the magnitude of the action potential overshoot It also shifts the threshold potential towards zero All of these actions combine to decrease excitability and conduction velocity They also account at least in part for the decreased responsiveness of partially depolarized fibers It is possible that procaine amide and quinidine also may decrease the rate at which the fast sodium channel is reactivated during repolarization, but appropriate studies on heart fibers are lacking

Repolarization of nerve fibers is delayed by procaine as a result of an effect on potassium conductance similar to that described for sodium conductance [29,30] Unfortunately repolarization of cardiac fibers is much more complex than is the case for nerve It may be that prolongation of the cardiac action potential by procaine amide and quinidine also results in part from a drug induced change in one or more of the membrane channels that permit efflux of potassium appropriate studies using voltage-clamp and other techniques are needed to clarify the matter

Phase 4 depolarization of normally automatic cardiac cells in the specialized atrial fiber tracts and His Purkinje system seems to result from a voltage and time dependent decrease in potas

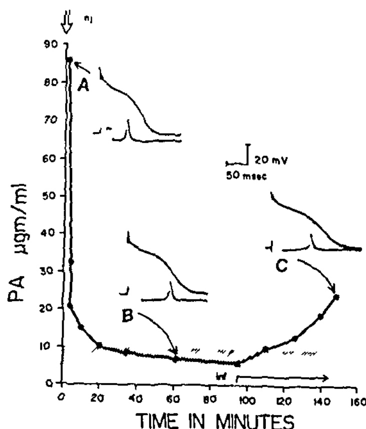


Fig 3 Effects of procaine amide on action potential characteristics of a blood superfused Purkinje fiber Vertical axis plasma procaine amide concentration µg/ml shaded area therapeutic concentration range horizontal axis time in minutes *A* shows a control action potential (*on the upper trace*) and a 200 V /sec calibration and measurement of V (*on the lower trace*) for an isolated Purkinje fiber superfused with the blood of an anesthetized dog The dog was then given a rapid intravenous injection of procaine amide 25 mg /Kg Following equilibration of the fiber at a therapeutic plasma procaine amide concentration (*B*) action potential duration was prolonged and amplitude and V were decreased Additional procaine amide was then infused to raise plasma levels to the toxic range (C) Further decreases in amplitude and V_{m} and prolongation of duration occurred (Modified after Rosen M R Gelband H and Hoffman B F ref 20)

action potential to be initiated at a higher more normal level of membrane potential The increase in membrane potential at the moment of excitation outweighs the direct effect of a low concentration of drug on inward sodium current and as a result the action potential improves and conduction velocity increases

The effects of quinidine and procaine amide on active responses of abnormal or depressed fibers have been described less completely In preliminary studies of isolated preparations of diseased human atrium, obtained as part of the routine cannulation procedure for cardiopulmonary by pass it has been shown that procaine amide in concentrations of 1 to 100 µg/ml exerts a variable effect on the action potential of specialized conducting fibers [4] In fibers with normal action potential amplitudes and upstroke velocities there is a dose dependent decrease in these parameters In partially depolarized fibers, having somewhat lower action potential amplitudes and upstroke velocities, there is a proportionately greater depressant effect of procaine amide However, in markedly depressed fibers, generating slow response action potentials which are exquisitely sensitive to low concentrations (0 1 to 1 µg/ml) of the calcium blocker verapamil even high concentrations of procaine amide have little or no effect [6]

B Effects on action potential duration and refractoriness It has been known for many years that both quinidine and procaine amide delay repolarization and increase the duration of refractoriness in atrial and ventricular muscle fibers similar effects are exerted on Purkinje fibers [1, 19] These direct effects are modified to some extent both by the ability of quinidine and procaine amide to attenuate the effects of catecholamines and acetylcholine on the myocardium and by any drug induced changes in rate

The effect on action potential duration also is influenced by [K] in that prolongation is more marked at lower values of [K] Also the magnitude of the drug effect on action potential duration varies with the anatomical location of fibers in the His Purkinje system The change is more marked for fibers initially demonstrating the shortest action potentials and less marked for those with the longest action potentials [19] The over all effect thus is to make more uniform the action potential duration over the entire length of the His Purkinje system

Prolongation of the action potential accounts only for part of the increase in duration of the effective refractory period caused by procaine amide and quinidine As described above procaine amide and quinidine decrease responsiveness and as a result prevent the generation of a new propagating action potential until repolarization has carried membrane potential to more negative values than were required before drug action [19] This decrease in responsiveness during repolarization is due in part to the effect of the drug on the maximum inward sodium current that can be generated at any level of membrane potential and perhaps in part also to a decrease in the rate of reactivation of the inward current

tive refractory period of the human atrium is significantly prolonged as is the ERP of the His Purkinje system Conduction in the His Purkinje system measured as the H V interval is slowed by 10 to 30 per cent as is conduction through the atrioventricular node Probably because of its vagolytic effect in these studies procaine amide shortened the ERP of the atrioventricular node and slightly increased sinus rate [35]

Mechanism for antiarrhythmic action

Since procaine amide and quinidine modify almost all aspects of cardiac electrical activity the range of possible mechanisms for antiarrhythmic action is immense Here it is possible only to mention a few of the more probable ones Many studies have shown that the likelihood of initiation as well as the likelihood of persistence of fibrillation depend in a critical manner on the number of cells in the population which are able to respond to a stimulus (the propagating impulse) at any particular instant Since both procaine amide and quinidine increase the effective refractory period of atrial and ventricular fibers (by decreasing the ability of incompletely repolarized fibers to generate an active response and by delaying the completion of repolarization) both agents may be expected to exert antifibrillatory action The finding that the atrial rate in both fibrillation and flutter decreases as a function of drug action suggests that quinidine and procaine amide do in fact slow the maximum repetition rate for any given cell until it no longer is possible for a circulating wave front of excitation to find a sufficient mass of excitable cells

The mechanism by which these drugs abolish premature depolarizations depends on the cause of the premature excitation If it results from firing of an automatic focus which employs the normal mechanisms we probably can assume that drug effect results from a suppression of the slope of phase 4 depolarization perhaps coupled with a shift in the level of the threshold potential towards zero If the premature depolarizations result from reentry it seems that abolition of the arrhythmia is due to a depressant effect of drug on the reentrant path such that an area of unidirectional block is converted into an area of bidirectional block [5] The most compelling evidence in support of this hypothesis comes from recent studies showing that procaine amide consistently and progressively increases the coupling interval of ventricular premature depolarizations before abolishing them [36] Unpublished observations show that quinidine has a similar effect

Antiarrhythmic action in the case of paroxysmal tachyarrhythmias is difficult to describe for all cases Nevertheless several points seem clear If the tachyarrhythmia results from reentry like that causing ventricular premature depolarizations procaine amide and quinidine might be expected to act by a similar mechanism Termination also might result from prolongation of the ERP in tissues just proximal to the site of reentry It is interesting to note that if these are the mechanisms of action one would expect the rate to decrease prior to termination of arrhythmia If a reentrant atrial rhythm results from participation of the atrioventricular or sinus nodes its persistence is critically dependent on an appropriate balance between conduction time in the node and refractoriness in the atrium Termination of arrhythmia could result either from depression of the reentering response in the node from prolongation of effective refractoriness in the atrium or from both

Other antiarrhythmic actions clearly are possible For example the ability of both drugs to decrease the slope of phase 4 depolarization in normally automatic cells can improve the responsiveness of these cells and in this manner could convert an area of depressed conduction with unidirectional block to an area of successful forward conduction Since the magnitude of the change in action potential duration caused by procaine amide or quinidine varies with the location of the fiber in the specialized conducting system this action also may contribute to antiarrhythmic action To clarify these possibilities new and careful clinical studies are needed

Treatment of toxicity

The toxic effects of quinidine and procaine amide on the cardiovascular system usually will disappear fairly rapidly if drug administration is stopped If treatment of drug toxicity is needed two types of intervention are possible Administration of sodium lactate by vein will diminish the toxic effects of both procaine amide and quinidine on the heart s electrical activity by lowering the plasma potassium level. For both drugs the intensity of effect on electrical activity is increased with increasing K concentrations In addition by changing plasma pH sodium lactate will

sium conductance There is evidence that when procaine amide diminishes the slope of phase 4 depolarization, there is no clear change in potassium conductance at the level of maximum diastolic potential[31] The mechanism by which procaine amide and quinidine act on automaticity of cardiac fibers thus remains unexplained A decrease in the slope of phase 4 depolarization can result from an increase in outward current, presumably carried by potassium, or a decrease in inward current, which might be carried by either sodium or perhaps calcium Each of these currents and the associated conductance, might be influenced by the two antiarrhythmic drugs

Effects on the heart and circulation

Quinidine and procaine amide exert many similar effects on the cardiovascular system For the most part these effects are dose related As mentioned above, when administered intravenously, quinidine strongly depresses the contractile function of the heart and causes a decrease in systemic vascular resistance This is brought about primarily by blockade of alpha adrenergic receptors These actions have markedly limited its administration by this route Procaine amide exerts similar but weaker effects on the heart and circulation although vasodilation probably is due mainly to ganglionic blockade During repeated intravenous injection of procaine amide in doses of 100 mg at intervals of 5 minutes blood pressure usually begins to show meaningful changes after a total dose of 600 to 800 mg[13] As might be expected in patients whose heart or circulation is compromised, decreases in output and blood pressure may occur at lower doses Since both quinidine and procaine amide decrease the contractility of the heart high blood levels may be associated with an increase in left ventricular end diastolic pressure The direct negative inotropic effect of quinidine contributes strongly to the cardiovascular depression and collapse which often result from intravenous administration of this drug Although both procaine amide and quinidine have been reported to attenuate the effects of the vagus on the mammalian heart evidence of this action in humans is not uniformly convincing

As might be expected from their effects on the electrical activity of single cardiac cells, quinidine and procaine amide cause dose dependent changes in the electrocardiogram which are clearly evident at therapeutic plasma levels[13,32] Both drugs also can cause abnormalities of cardiac rhythm and conduction Procaine amide, at plasma levels between 5 to 10 µg/ml, has little predictable effect on sinus rate or sinus rhythm However, the P R interval is slightly prolonged and this change is comparable in patients with normal and with slowed atrioventricular transmission QRS duration also increases as a function of plasma level and may be prolonged by 5 to 10 msec at a plasma level of 10 µg/ml Therapeutic levels of procaine amide usually do not prolong the QRS beyond the normal range Q T intervals corrected for heart rate are increased by procaine amide as a result of effects on ventricular action potential duration and conduction

Quinidine is likely to increase sinus rate because of the reflex sympathetic response to its hypotensive effect Like procaine amide, quinidine increases the P R interval QRS duration, and Q T interval During chronic oral administration it has been shown that the prolongation in QRS is dependent on plasma level at values > 2 µg/ml and can be clearly demonstrated within the entire therapeutic range[5] The increase in Q T duration caused by quinidine is more marked than that caused by procaine amide and is easily detected at therapeutic levels When the Q T interval is prolonged before drug treatment and there are early premature ventricular depolarizations, or when the coupling of the VPDs is unusually short in the presence of a normal Q T interval administration of quinidine may be associated with increased risk because of the production of the R on T phenomenon[33] The magnitude of the effect of quinidine on QRS duration does not seem to be dependent on the initial value These findings for humans agree well with data reported for studies on conscious dogs[34]

High plasma levels of either procaine amide or quinidine can cause high grade atrioventricular block, asystole, ECG patterns resembling bundle branch block, other conduction abnormalities and ventricular arrhythmias including premature depolarizations tachycardia, and fibrillation Excessive prolongation of the QRS complex (> 35 per cent) usually indicates that more serious toxic effects are imminent

Studies on humans using catheter electrodes[35] have confirmed most of the actions demonstrated for procaine amide in experiments on laboratory animals At therapeutic plasma levels the effec

A QRS-phase progression indicator

In a previous paper the inscribing directions of planar QRS loops have been correlated to the phase progression of the QR or RS segment in leads of the same plane The method requires the determination of the latter by inspection It yields a rate of success of 86 per cent or better when applied to

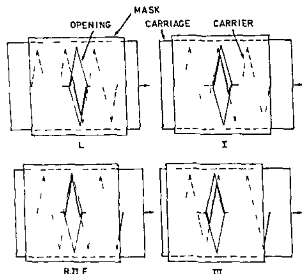


Fig 1 A prototype of the QRS phase progression indicator showing the QRS carrier wave on the sliding carriage and the mask with a diamond shaped opening This series of four frames depicts the six QRS waveforms by moving the carriage to the right—a case of forward phase progression in the *sequence of Leads L, I –R II F through III*

published material. A visual aid to facilitate the rapid *determination of phase progression* in a group of leads is introduced This device consists of a sliding carriage on which the fundamental QRS "carrier wave" is drawn and a stationary mask with a diamond shaped opening Both can be made of cardboard or similar material The carriage can be manually slid and adjusted under the mask so that slightly over one half cycle of the carrier wave of the QRS is framed within the opening at all times Moving the carriage relative to the mask will change the framing i.e the phase of the carrier relative to the frame so that various QRS waveforms can be represented Both the leading and trailing edges of the frame itself form parts of the QRS As shown in Fig 1 for example if one can simulate the whole series of QRS waveforms of a sequence of Leads L, I –R II F and III for a given subject by sliding the carriage to the right in successive steps then this is a case of forward phase progression in such lead sequence On the other hand a backward phase progression would require the carriage to move in the opposite direction

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Of a normal old man

The physician is regularly asked to determine if a person is normal. This he does and he is prepared to defend his decision This decision is made for children young adults and middle aged adults But when does the physician cease to consider a person abnormal merely because he is aging? What are the criteria for normal for an old person? Or can an 80 or 90-year-old man be normal? When degeneration of function of an organ system is merely the response to aging is that function normal for that age or is it abnormal? These are some of many important geriatric questions—Do we have answers?

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increase the binding of quinidine to albumin and thus decrease the free drug level acting on the heart Administration of beta adrenergic amines also will diminish the undesirable changes in electrical activity caused by quinidine and procaine amide and at the same time will help to attenuate any negative inotropic effect exerted by either agent

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Annotations

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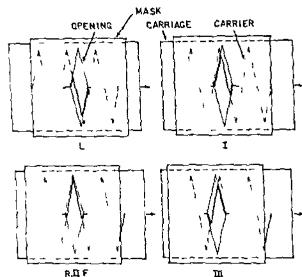


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Of a normal old man

The physician is regularly asked to determine *if a* person is normal This he does and he is prepared to *defend his* decision This decision is made for children young *adults and* middle aged adults. But when does the physician *cease to* consider a person abnormal merely *because he* is aging? What are the criteria for normal *for an old person*? Or can an 80 or 90-year-old man be normal? When *degeneration* of function of an organ system is merely the response *to aging* is that function normal for that age or is it abnormal? These are some of many important geriatric questions—*Do* we have answers?

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Urography in acute renal failure

In 1963 Schwartz Hurwit and Ettinger showed that excretion urography could be used in patients with renal failure to define the shape and size of the kidneys and to diagnose or exclude extrarenal obstruction Since then high-dose urography has become widely accepted as a valuable part of the routine investigation of patients with renal failure (reviewed in 1971) However severe the renal failure opacification of the renal substance is almost always sufficient to define the renal outlines and there is almost always enough visualization of the pelvicalyceal system to define or exclude obstruction This is true even in patients presenting acutely with oliguria or anuria

A recent report suggests that urography may prove to be of further value in patients with acute renal failure by helping to establish the diagnosis of acute tubular necrosis (ATN) The report describes the appearances during excretion urography in 32 patients with nonobstructive acute renal failure twelve of whom were anuric and ten oliguric The study was mainly concerned with the degree of opacification of the renal substance by contrast medium during the course of excretion urography (the nephrographic pattern)

In normal subjects the nephrogram is most dense at the end of injection fading quickly as the blood level falls In each of twelve patients with uncomplicated ATN there was an obvious immediate nephrogram which instead of fading persisted for up to 24 hours or more This observation confirms in a clinical setting reports of the same abnormal nephrographic pattern in rats with acute renal failure induced by vascular clamping or mercury poisoning The same nephrographic pattern was also observed in three out of five patients in whom oliguric renal failure was due to acute suppurative pyelonephritis It has not been reported in any other conditions

The remaining patients showed differing abnormalities of the nephrographic pattern but because of the small number of patients it was not possible to assess the significance of the appearances except in as much as they excluded the diagnosis of uncomplicated ATN Two patients were of particular interest since the clinical diagnosis was one of uncomplicated ATN Instead of the expected immediate obvious persistent nephrogram both showed only a faint nephrogram initially which gradually became more dense over the next 24 hours In both patients the ATN was complicated by antecedent kidney disease in one case renal amyloid in the other case chronic glomerulonephritis

If these abnormalities of the nephrographic pattern are confirmed excretion urography will clearly be of value in the management of patients with acute renal failure In this condition both short term and long term treatment depend on whether the lesion is potentially reversible e g uncomplicated ATN or irreversible e g cortical necrosis fulminating proliferative glomerulonephritis etc In many patients the clinical picture may be so typical that no further investigation is required In others there may be doubt Renal biopsy can provide a histologic diagnosis in many cases but should not be undertaken lightly because of the increased hazard of hemorrhage in such patients Furthermore biopsy may not be conclusive in patients with ATN and a retrospective diagnosis may have to wait upon recovery after weeks of dialysis. If urography can establish a diagnosis of uncomplicated ATN in the first few days it will remove uncertainty from the management of this type of patient

One word of caution Urography was previously considered dangerous in patients with renal failure because it appeared occasionally to be responsible for severe deterioration in renal function More recent studies[•] have suggested that this is not so provided the patient is not clinically dehydrated at the time of examination and fluids are not restricted This is particularly important in patients with acute renal failure In practice it means that prerenal failure must be excluded before urography It must also be emphasized that most patients with acute renal failure are seriously ill at the time of presentation and many will require immediate dialysis If good results are to be obtained and if the patient is not to be put at risk excretion urography should only be undertaken when there is the closest cooperation between radiologist and clinician

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Smoking and cardiovascular disease

In Dr Geoffrey Rose s recent paper in this JOURNAL (AM HEART J 85 838 1973) he mentions an ongoing controlled clinical trial designed to demonstrate the benefits of stopping smoking The results of that trial may or may not resolve some of the many uncertainties and dissentions about the relationship of smoking and coronary heart disease (CHD) In the meantime however the scientific community must form its opinions from the available epidemiologic evidence about the association of smoking and CHD and about the possibility that a cessation of smoking will prevent CHD Unfortunately Dr Rose s presentation of that evidence is neither balanced nor accurate

Dr Rose has omitted any reference to data or viewpoints that contradict his beliefs In a multinational study Keys found no association between cigarette smoking and CHD in the countries of Finland The Netherlands Yugoslavia Italy Greece and Japan In a separate study in Yugoslavia the United States Public Health Service also found no association between cigarette smoking and CHD In an analytic review of epidemiologic data I noted that angina pectoris as the sole manifestation of CHD is probably unrelated to cigarette smoking I also pointed out that the alleged rising gradient of CHD mortality with the amount and duration of cigarette smoking is not consistent and is in some instances, actually reversed Furthermore the data on discontinuation of cigarette smoking show such contradictory and inconsistent findings that they frustrate all attempts to argue from effect to cause Data analyses of diverse investigations including those of Doll and Hill s British doctors Kahn s analysis of the Dorn United States veterans data Hammond s American men and women and the Framingham study comparing smokers and discontinued smokers all indicate that disability and death from CHD had little if any association with continued cigarette smoking in people aged 65 and over—a group of the population containing over two thirds of all CHD deaths The Framingham study investigators in noting that the effects of smoking are limited to those persons predisposed by an already compromised circulation " have discounted along with Keys, the role of smoking in atherogenesis. In an international symposium on twin registries in the study of chronic diseases the inconsistent findings made the participants unwilling to accept a causal role for cigarette smoking in relation to cardiovascular diseases Unless these inconsistencies and conflicts in the data are satisfactorily disproved or reconciled, the current hypothesis for cigarette smoking as a major risk factor in CHD must be re-examined and alternatives must be sought.

In assuming a causal relationship between smoking and CHD Dr Rose ignores alternative mechanisms that have been suggested by other investigators In particular he neglects the constitutional hypothesis, which states that the self selected group of people who choose to smoke are also more vulnerable to CHD than nonsmokers This hypothesis is supported by evidence indicating that smokers and non smokers differ in morphology physiology biochemistry personality and way of life Kety has pointed out that "genetic factors also operate significantly in the tendency to smoke That genetic factors also operate in the development of CHD is generally well accepted but Dr Rose failed to mention several important studies in which the relationship of genetics smoking and CHD has been examined

In the Swedish twin pair study after finding no essential difference for "angina pectoris in monozygotic twin pairs discordant for smoking the investigators concluded that this evidence provides support for the importance of constitutional factors as against the importance of cigarette smoking in the development of angina pectoris. In a similar study involving United States veteran twin pairs the results revealed no association between smoking and cardiovascular symptoms among smoking-discordant monozygotic twin pairs" Here too the authors concluded that the absence of association among the monozygotes and its presence among the dizygotes and unmatched pairs strengthens the case for a constitutional hypothesis Additional cogent evidence was recently supplied by Swedish investigators who found no mortality differences in monozygotic twin pairs discordant for smoking habits. Thus when heredity was accounted for the mortality differences in dizygotic twin pairs between smokers and nonsmokers were no longer apparent

The cardiac efficacy of an antismoking intervention is also uncertain At a time when the percentage of cigarette smokers among British doctors fell about 50 per cent mortality for CHD rose about 8 per cent Cornfield and Mitchell in a pessimistic analysis of the feasibility of achieving conclusive results from intervention studies stated that "there is no certain basis for computing the magnitude of the reductions that might be achieved or even indeed of being sure that reductions are achievable " This view does not lend encouragement to Dr Rose s expectation that the controlled intervention study in London will settle th question of whether stopping smoking will lower CHD rates Complex problems are created by the issues of confounding variables and by what may be called the associated intervention effect The latter effect arises because persons in a free living society who quit smoking also tend to modify other variables (including other so-called risk factors) that may have independent effects on CHD incidence For these reasons the London trial may provide suggestive results but the effects due to cessation of smoking may be difficult or impossible to disentangle from the effects of the confounding variables The same problem applies to the extensive Multiple Risk Intervention Trials now planned in this country In these trials intervention in smoking habits is only one part of the program it also contains simultaneous dietary changes and treatment of hypertension Because the intervention is multiple the independent contributions of the individual factors cannot be meaningfully analyzed

The history of medicine throughout the centuries contains many examples of evangelical fervor for etiologic or therapeutic theories that were later shown to be wrong A prime responsibility of epidemiologists is to maintain the skepticism of science amidst the passions of evangelism If smoking is

related to CHD in only a limited segment of the population the people who are not at risk will hardly be benefited by blunderbuss interventions aimed at everyone If smoking is not causally related to CHD the true situation will never be discerned unless investigators observe the cardinal scientific principle of ruling out counter hypotheses Until conclusive proof is available the health of the public and the welfare of science demand a balanced consideration of all the available evidence

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Letters to the Editor

Sinus rhythm after prolonged atrial fibrillation complicated by sinus arrest and syncope

To the Editor

Spontaneous return of sinus rhythm after prolonged atrial fibrillation in rheumatic heart disease has recently been reported in three patients who spontaneously reverted to sinus rhythm after having atrial fibrillation for over ten years The unusual occurrence had no satisfactory explanation according to the authors All developed first degree block with return of sinus rhythm Six other cases of prolonged atrial fibrillation spontaneously returning to sinus rhythm have been described In Lewis three cases the return of sinus rhythm was associated with first degree block in two Fogel s case and Burch s case had a normal PR interval but Vaisrub s case was also prolonged None of these nine cases had symptoms from conduction difficulties

We recently treated a patient with documented atrial fibrillation for 15 years who spontaneously reverted to sinus rhythm 11 years after closed mitral commissurotomy She then developed intermittent sinus arrest and syncope requiring a permanent pacemaker

Atrial fibrillation occurs when the atrium is inhomogeneous with regard to excitability recovery and conductivity Biopsies in patients with chronic atrial fibrillation have generally shown abnormalities and non uniformities in resting membrane potential, conduction velocity and excitability Local areas of block were common Pathological studies of patients with atrial fibrillation have shown decrease in sinoatrial node muscle fibers damage to internodal tracts and occasionally blockage of the arterial supply to the SA node Varying degrees of damage to the muscle fibers have been noted as well as varying degrees of fibrosis In some severe fibrosis is found along with disruption of architecture and muscle replacement with fibrous tissue These changes are the pathological basis for the electrophysiological abnormalities associated with atrial fibrillation Holzmann reported a case of atrial fibrillation spontaneously reverting to sinus rhythm At autopsy the left atrium was converted into a fibrous sac He believed that initially the atrial fibrillation was triggered by left atrial involvement and that conversion to sinus rhythm occurred when all of the left atrial myocardium was destroyed

The pathological changes as previously described by Bailey and colleagues, Singer and associates Hudson and Davies and Pomerance make understandable both the development of atrial fibrillation in association with chronic rheumatic heart disease as well as the spontaneous conversion to sinus rhythm and the possibility of sinus arrest We would be surprised if more cases are not described in the future with bradyarrhythmias complicating the return to sinus rhythm after prolonged atrial fibrillation in chronic rheumatic heart disease

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Congenital absence of circumflex coronary artery

To the Editor

We read with much interest the article entitled *Congenital absence of the circumflex coronary artery Clinical and cineartenographic observations* by Barresi and associates (AM HEART J 86 811 1973) We are fully aware of the *different* interpretations made by the original authors and by Page and colleagues in regard to the diagnostic validity of the two cases presented We have considerable experience with detailed anatomical and postmortem angiographic studies of coronary arteries and would like to provide an alternative explanation which might help clarify this controversy

1 True congenital absence of circumflex artery has not been mentioned as an entity in the larger series of anatomical studies of coronary patterns Hypoplasia of a major coronary artery does occur but is much rarer than an anomalous circumflex artery originating from the right sinus of Valsalva or from the most proximal portion of right coronary artery According to Ogden this is the most common form of minor congenital variation of coronary artery In the past five years we have seen only one example of hypoplastic left circumflex artery in conjunction with an extremely dominant right coronary artery in 707 consecutive cases Congenital absence of the circumflex artery was not present in any of these cases

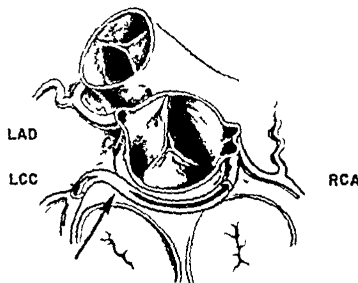


Fig 1 An example of complete occlusion of anomalous left circumflex artery by atherosclerosis (*arrow*)

2 Congenital anomalous left circumflex arteries may not show any radiological opacification in cases where there is total atherosclerotic occlusion Two such cases studied in our laboratory demonstrated complete obstruction in the first three centimeters (Observe *arrow* Fig 1)

Although we can not with certainty rule out the possibility of congenital absence of the circumflex artery as described by Barresi and colleagues we wish to point out the alternative possibility of the presence of congenital anomalous circumflex arteries occluded by atherosclerotic lesions which can not be demonstrated roentgenologically

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Reply

To the Editor

The thoughtful comments of Drs Liu and Lupton are appreciated It is clear that an anomalous circumflex artery which was flush-occluded at its origin would not be visualized radiographically A vessel which was diseased or even totally occluded at some point beyond its origin ought to be accessible for selective visualization This was ruled out since no ostial lesions or occluded stumps were seen in any of the aortic root injections or selective cusp injections, in either of our patients. Furthermore no collateral vessels to the area of supply of the circumflex artery were seen and in each of the patients all blood supply could be accounted for by the visualized vessels which appeared normal in our estimate

We hypothesize congenital absence of the circumflex artery for the following reasons

1 Our angiograms excluded anomalous origin of a normal circumflex artery

2 No occluded stumps" were seen on cusp injections.

3 There were no collaterals with retrograde filling of any occluded vessel

However the possibility of atherosclerotic occlusion of an anomalous circumflex artery as suggested by Drs Liu and Lupton is probably the only alternative explanation for the findings in our two patients but this will obviously remain unproven short of pathologic examination

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Book reviews

Aorto-coronary Bypass Surgery By B Buis Leiden Holland 1974 H E Stenfert Kroese N V., 80 pages. Paperbound

Buis of the Department of Cardiology of Leiden University Hospital concisely reviews in this paperback, the medical literature and the experience at Leiden with coronary bypass surgery The illustrations of coronary angiograms are excellent The results of surgery indications and contraindications are clearly stated The experience at Leiden with coronary bypass surgery appears to be comparable to that of most of the larger centers of the world Cardiologists and cardiovascular surgeons will be especially interested in this lucid discussion

Advances in Cardiology Vol 13—Comparative Pathology of the Heart Edited by Homburger and Lucas Basel 1974 S Karger AG 379 pages 136 figures 39 tables Price $95 00

This is another excellent volume of Advances in Cardiology The problems considered range widely from diseases of the blood vessels to those of the heart However the emphasis is on myocardial disease e g cardiomyopathies myocarditis cardiac muscle pathology and morphology and viral arteritis The contributions are concerned primarily with comparative pathology of the heart Several presentations are on atherosclerosis This issue is a very important one and is particularly timely It is an interesting source of information and is highly recommended. The various issues of Advances in Cardiology are worth owning but the price is high for this one

Cardiovascular Physiology Edited by A C Guyton and C E Jones, Baltimore 1974 University Park Press 349 pages

This review of cardiovascular physiology by Guyton and Jones covers interesting and important aspects of the circulation The contributors review very successfully the important developments in the circulation For example among the problems discussed are mechanics of the circulation myocardial excitation and contraction the pulmonary circulation nervous control of the circulation cardiac output and shock and control of arterial blood pressure The presentations are lucid and brief whereas the bibliographies are rather extensive This is an excellent review of some of the fundamental principles of physiology of the circulation

Sudden Death and Coronary Heart Disease By Sidney Goldstein M D New York 1974 Futura Publishing Company 213 pp Price $15 00

This small book on an important and intriguing subject is well written and easy to read It is of course primarily concerned with coronary artery disease and although this is the most common cause of sudden death in the United States, there are many other interesting and puzzling causes of sudden death other than coronary heart disease Goldstein reviews the problems in a conventional manner The chapters on pathogenesis are most important as are the points for attack to prevent sudden death Yet these discussions are rather brief Electrophysiologic mechanisms are suggested which result in sudden death These concepts are generally accepted but certainly not fully established The author strongly suggests that exercise will prevent sudden death but this reviewer knows of people who have died while exercising Certainly the role of exercise in modifying coronary circulation remains unknown even though exercise is suggested strongly to prevent sudden death by improving the coronary circulation The 15 chapters and the preface by Dr M F Oliver are interesting and consider sudden death very well for all physicians This book should be read by all physicians

Congenital Diseases of the Heart By Abraham M Rudolph M D Chicago 1974 Year Book Medical Publishers Inc 656 pp Price $?5 00

This book on congenital heart disease is written primarily for teaching It is directed at undergraduate medical students interns, and residents and physicians in pediatrics who wish to learn clinical cardiology The book is planned to correlate structural changes with associated hemodynamic alterations and clinical manifestations and with management. The diagrammatic illustrations are clear and simple and present the concepts extremely well. Dr Rudolph must be a good teacher as this book seems to reflect As would be expected the book includes embryology hemodynamic changes and methods of study of the common congenital cardiac defects The author properly emphasizes the bedside approach to diagnosis and management The book is highly recommended

Books received

The Gods of Life By Neil Elliott New York 1974 Macmillan Publishing Company Inc 180 pp Price $7 95

The Year Book of Medicine 1974 By D E Rogers R M Des Prez P Heller F Braunwald N J Greenberger P K Bondy and F H Epstein Chicago 1974 Year Book Medical Publishers Inc 704 pp

Vectorcardiography Self Assessment By Edward K Chung M D Hagerstown Md 1974 Harper & Row Publishers Inc 114 pp Price $12 95

Platelet Aggregation and Drugs Edited by L. Caprino and E C Rossi New York 1974 Academic Press Inc 298 pages Price $15 25

The Diagnosis of Bleeding Disorders second ed By Charles A Owen Jr M D Ph D E J Walter Bowie M.A B.M F A C P and John H Thompson Jr Ph D., Boston 1975 Little Brown & Company 398 pages

Principles and Techniques of Human Research and Therapeutics vol III Pharmacokinetics Drug Metabolism and Drug Interactions Edited by F Gilbert McMahon M D Mount Kisco N Y 1974 Futura Publishing Co Price $14 00

Principles and Techniques of Human Research and Therapeutics vol V Cardiovascular Drugs Edited by F Gilbert McMahon M D Mount Kisco N Y 1974 269 pages Price $15 00

Announcements

Purdue Defibrillation Conference

The Biomedical Engineering Center of Purdue University will hold a conference in Lafayette Indiana from October 1 to 3 1975 covering the practical and clinical aspects of cardiac defibrillation The speakers have been selected based upon their positions as leaders in their respective fields The topics to be discussed include clinical basic science and engineering aspects of electrical defibrillation as it pertains to the needs of physicians nurses emergency medical personnel hospital engineers equipment manufacturers and research scientists

The state of the art of defibrillation techniques will be presented and examined critically and a major goal of this three day conference will be to integrate all available technology for optimization of ventricular defibrillation The registration fee of $95 includes admission to the proceedings and two luncheons.

For further information please write Division of Conferences and Continuation Services Stewart Center Purdue University West Lafayette Indiana 47907 Telephone (317) 749 2533

American Heart Journal

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Editorial

Repetitive supraventricular tachycardias in context

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Although in everyday practice palpitation is a frequent complaint, it is not always documented that this subjective sensation is due to a rapid ectopic rhythm. The newer techniques of ambulatory electrocardiographic monitoring and of intracardiac stimulation and recording have given a deeper insight into the natural history of repetitive supraventricular tachycardia (RSVT). This arrhythmia may be troublesome at any age either in normal subjects or in patients with congenital heart abnormalities or rheumatic heart disease. Follow-up of normal individuals with RSVT has shown that late in life they, as anybody else, can develop co-existing coronary atherosclerosis or primary conducting system abnormalities (sclerosis of the left side of the cardiac skeleton or bilateral bundle branch fibrosis). These associations pose additional diagnostic and therapeutic problems.

RSVT frequently occurs in persons with ventricular pre-excitation. The latter should be suspected in any individual with a history of long-standing recurrent rapid ectopic atrial rhythms. Pre-excitation is said to be present when a sinus (or atrial) impulse arrives at a portion or all of the ventricular mass earlier than expected if the impulse had been conducted through the normal A-V pathways at the usual speed.

A short (0.12 sec. or less) P-R interval and a wide QRS complex are seen in Wolff-Parkinson-White syndrome (WPW), presumably due to a total bypass of the normal A-V pathway. However, the P-R interval can be normal in the presence of atrial enlargement or intra-atrial conduction defect. Since some normal individuals have short P-R intervals and narrow ventricular complexes, the Lown-Ganong-Levine (LGL) syndrome (presumably due to a total or partial A-V node bypass) can be diagnosed with certainty only when RSVT (or rarely, atrial fibrillation) is present. It should be kept in mind that unilateral or bilateral bundle branch block can widen the QRS complex and even normalize the P-R interval.

In the majority of patients with the LGL syndrome, His bundle electrograms show a short A-H interval. However, what characterizes this syndrome is, from the clinical viewpoint, the presence of RSVT, and from the electrophysiologic aspect, the response to atrial pacing at progressively higher rates. Caracta and co-workers have indicated that persons with LGL syndrome showed three types of responses using this procedure. Most responded to atrial pacing as did normal subjects but the magnitude of increase

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in A H intervals was less In others there was some degree of A H prolongation at the slower rates which was followed by a plateau response at faster rates and, finally, a further increase at even higher rates Rarely, atrial pacing did not increase the A H intervals

We believe that the definition of the LGL syndrome should not be given only in terms of absolute measurement of static intervals but extended to include the dynamic response to atrial pacing [2] It is a matter of semantics whether subjects with RSVT, normal P R, borderline low (but nevertheless normal) A H, narrow QRS complexes and an abnormal response to atrial stimulation should be considered as having the LGL syndrome [2] Conceptually, they probably have a partial bypass of the A V node In any case, the treatment is probably the same even if the mechanism were to be a functional longitudinal dissociation of the A V node

RSVT is a paroxysmal arrhythmia usually beginning abruptly with a premature beat The underlying mechanism is generally an A-V reciprocation involving a single anatomic structure (A V node) or two (and more rarely even three) distinct electrophysiologic pathways More than one circuit might be present in the same person

Premature depolarization of the atria associated with a prolonged A V conduction time is the event which *triggers* the reciprocating tachycardia Some authors using statistics obtained before the era of ambulatory electrocardiographic monitoring, considered that premature atrial beats were more frequent in patients with WPW syndrome than in the normal population [3] On the other hand, experience with the Holter instrument suggests that atrial extrasystoles are common in persons without clinically detectable heart disease [3] Besides the triggering premature atrial depolarization need not be an atrial extrasystole in the strict sense since marked sinus arrhythmia and retrograde conduction to the atria (from a ventricular beat) can produce the same effect Hence, fluctuations in heart rate which are of everyday occurrence (and which at the most only produce the well known "skipped beat sensation) can be more significant in subjects with pre excitation [3]

The treatment of RSVT should be viewed in two phases abolishment of the arrhythmia when present and prevention of its recurrence Since at least parts of the A V node are used in nearly all reciprocating A V circuits, treatment of established tachycardias is conventional and does not pose great problems A more difficult task is preventing recurrence of the arrhythmia Follow up of patients with long standing RSVT shows that over the years the treatment of choice of sporadic attacks (in absence of organic heart disease) is supportive therapy by the physician The affected individuals should be taught to live with their problems and how to use to their advantage the different vagal maneuvers that abolish the tachycardias

It has been noted that there are periods of time usually precipitated by stressful life situations, or overuse of stimulant drugs and beverages during which the frequency and severity of the paroxysms increase Surprisingly, in some of these persons this symptomatology is no longer seen after a few days or weeks of reassurance, sedation and propranolol therapy Admission to a hospital although desirable is not necessary Thereafter, they revert to their usual patterns of RSVT

In other cases, or in presence of associated heart disease, more energetic measures are required Most patients receive not only propranolol but digitalis, quinidine and procaineamide generally in combination Lack of success in ambulatory patients is due to patient compliance or socioeconomic reasons especially when the arrhythmia occurs at frequent intervals which require continued use of drugs The physician should be aware of these factors when prescribing drugs that might have to be used as long as the person lives

Specialized electrophysiologic studies are justified whenever the arrhythmias cannot be controlled medically Conventional catheterization techniques help in assessing co existing heart disease Intracardiac recordings during electrical stimulation permit the identification of the type(s) of pre excitation (if present) the mechanisms of the arrhythmias and the functional properties of both normal and accessory pathways [4] These studies are less useful in determining the anatomic location of the accessory pathway(s) and the effects of *orally* administered drugs on the latter, as well as on the A V node

Permanent QRS inhibited ventricular demand pacing has been used to prevent undesirable bradycardia in some patients receiving beta blocking agents In some persons with mild or unrecognized forms of depression the dose

required to prevent recurrence of the arrhythmia might make the psychological symptoms worse the physician then has to decide what is more important the cardiovascular or psychological dysfunction

More complicated types of implantable pace makers such as the sequential atrioventricular demand (bifocal) units should be used only after performing specialized electrophysiologic studies We agree with those who have stated that there is no universal pacer that can suit all patients with RSVT[5,6]

Several authors have implanted pacemakers which could be activated externally during bouts of tachycardia usually by magnets or radiofre quency signals These have included conventional QRS inhibited ventricular demand units rapid atrial stimulators atrial scanner pacers and atrial or ventricular triggered pacemakers with preselected coupling intervals Surgery has been performed in some patients with WPW syndrome and intractable arrhythmias In these cases epicardial mapping is essential in addition to catheter studies Success has been achieved in both types B and A[7]

Although we have limited this discussion to RSVT it should not be forgotten that patients with any type of pre excitation can also have attacks of recurrent atrial fibrillation Rapid life threatening ventricular rates occur in patients with WPW as well as with LGL syndrome when the effective refractory period of the accessory pathway is extremely short This is especially true in the presence of co existing organic heart disease Thought provoking information regard ing these arrhythmias was recently presented elsewhere[2,8] But that is another story

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Clinical communications

The use of noninvasive methods in the evaluation of left ventricular performance in coronary artery disease

I Relation of systolic time intervals to angiographic assessment of coronary artery disease severity

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Selective coronary arteriography and left ventricular angiography are the definitive procedures for the evaluation of coronary artery disease and its effect on the left ventricular myocardium[1-3] Noninvasive techniques for the evaluation of left ventricular function could be of value in subsequent follow up of patients undergoing treatment for coronary artery insufficiency whether surgical or medical[4, 5]

There has been increasing use of the noninvasive technique of systolic time interval (STI) determination for study of left ventricular function in various conditions of left ventricular abnormality[6-10] This method is atraumatic rapidly performed, inexpensive and well suited to frequent patient evaluation Its results have been found to correlate well with both directly determined STI and angiographically determined indices of left ventricular performance[8-12] Recent studies have indicated that externally determined STI reflects acute changes in performance in angina pectoris[12, 1]

This study was designed to evaluate left ventricular performance by means of STI in conjunction with coronary arteriography and left ventriculography in a series of patients with clinical evidence of coronary artery disease (CAD) Its results will be the basis for subsequent serial investigation of these patients by STI following either medical or surgical treatment of their condition

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Materials and methods

A total of 113 patients with possible CAD each had STI determination immediately prior to coronary and left ventricular cineangiography for the evaluation of chest pain There were 87 men and 26 women, ranging in age from 25 to 69 years, the mean being 51 ± 8 years No patient had sustained an acute myocardial infarction (AMI) within the 3 months prior to his study no patient had left bundle branch block, anterior or posterior hemiblock or aberrant ventricular conduction, no patient had hypertensive or valvular heart disease

STI were measured from the simultaneous recording of the electrocardiogram (ECG) phonocardiogram (PCG), and indirect carotid artery pulse tracing (CAR) by an Elema Schonander Mingograf recording system at a paper speed of 100 mm per second using previously described techniques[8] The standard limb lead of the ECG which described the earliest QRS deflection was recorded (usually Lead II), the heart sounds were recorded at 100 and 400 Hz by an Elema Schon

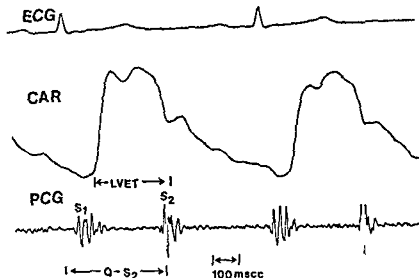


Fig 1 Durations of systolic time intervals simultaneous recording of ECG PCG and external CAR at a paper speed of 100 mm per second

ander EMT 25B piezoelectric accelerometer microphone placed at the right upper sternal border the carotid artery pulse tracing was obtained by manually holding an Elema Schonander piezoelectric transducer over the common carotid artery Recordings were performed between the hours of 0630 and 1000 and the patients were studied in the supine position at rest

The durations of the STI were determined as follows (Fig 1) Total electromechanical systole ($Q-S_2$) was measured from the initial QRS deflection of the ECG to the initial high frequency vibrations of the aortic component of the second heart sound on the PCG the left ventricular ejection time (LVET) was measured on the indirect carotid artery pulse tracing from the point of onset of rapid upstroke to the trough of the incisura the pre ejection phase (PEP) was indirectly obtained by subtracting the LVET from the Q S_2 the heart rate was derived by measuring the R R interval on the ECG Each of these intervals was measured to the nearest 5 msec in at least five consecutive and 10 total cardiac cycles and the mean of each interval was taken as the representative length In cases of markedly irregular rhythm interval measurements for more cycles were averaged The reproducibility of recording was studied by two methods, each of which satisfactorily demonstrated reproducibility in the recording and determination of the STI randomly selected patients received repeated studies by a second investigator and randomly selected recordings were analyzed independently by each of two investigators

The STI were then corrected for heart rate and sex according to the regression equations of Garrard Weissler and Dodge[9] thus yielding indices Q S_2I PEPI and LVETI The ratio of PEP to LVET (PEP/LVET) was determined by dividing the uncorrected PEP by the uncorrected LVET

All patients underwent selective coronary and left ventricular cineangiography according to the techniques of Sones and Shirley[16] and Lehman[17] respectively Angiographic evidence of greater than 70 per cent arterial obstruction in any major coronary artery system was considered to document significant vessel disease [8] and a significant left main coronary artery lesion was considered to represent two vessel disease Thus any patient could have zero one two or three vessel disease

The left ventricular end diastolic pressure (LVEDP) was obtained with a Statham P 23dB transducer and the left ventricular ejection fraction (LVEF) was computed from the left ventriculogram according to the volume estimation of Greene and associates [9] Volumes were computed in end-diastole and end systole and their difference the stroke volume was divided by the end diastolic volume to derive LVEF Normal LVEF was considered to be 0 67 ± 08 [20] The left ventricular wall motion (LVWM) was judged either

Table 1 Individual clinical, hemodynamic, and STI data according to coronary arteries diseased

	Clinical					Hemodynamic			STI			
Patient	Age	Sex	Prior AMI	CHF	Meds*	LVEDP	LVEF	LVWM	Q S$_2$I	LVETI	PEPI	PEP/LVET
0 V												
1 D A	40	M	0	–	–	15	0 67	Abnormal	527	406	120	0 33
2 R B	33	M	1	–	–	9	0 85	Normal	515	419	95	0.2[illegible]
3 J B	50	M	0	+	–	7	0 84	Normal	534	399	136	0 40
4 L. B	49	F	0	+	DP	–	–	–	542	380	162	0 48
5 J C	38	M	0	–	–	11	0 75	Normal	529	413	117	0 30
6 B E	55	M	0	–	–	12	0 82	Normal	549	440	109	0.25
7 J G	53	M	0	–	–	4	–	–	555	405	150	0 4[illegible]
8 G G	49	F	0	–	–	11	0 77	Normal	566	419	137	0 34
9 J H	56	F	0	–	–	4	0 80	Normal	530	410	120	0 31
10 H J	51	M	0	–	DP	4	–	–	519	386	133	0 39
11 T J	53	F	0	–	–	16	0 75	Normal	546	409	137	0 38
12 L. J	25	M	1	–	–	16	0 81	Normal	521	409	112	0 29
13 G J	40	M	3	–	P	10	0 86	Normal	547	405	138	0 39
14 M K	40	F	0	–	–	9	0 78	Normal	562	444	122	0 [illegible]9
15 R M	50	F	0	–	–	24	–	–	544	378	166	0 57
16 N M	42	M	0	–	–	6	–	–	547	403	134	0 39
17 R N	66	F	0	+	D	26	0 14	Abnormal	549	352	197	0 56
18 G P	52	M	0	–	–	18	0 70	Abnormal	542	406	136	0 37
19 P P	42	M	0	–	–	7	0 91	Normal	530	409	120	0 33
20 C R	26	M	0	–	–	11	0 75	Normal	539	404	135	0 37
21 H S	61	F	0	–	P	–	–	–	550	406	144	0 [illegible]8
22 P S	45	F	0	–	–	12	–	–	548	427	131	0 33
23 G S	52	F	1	–	–	13	0 78	Normal	606	445	161	0 36
24 M T	44	F	0	–	–	14	0 79	Normal	542	407	135	0 37
25 G V	51	F	0	–	–	15	0 92	Normal	561	413	148	0 39
1 V												
1 J A	51	M	1	–	–	21	0 28	Abnormal	524	374	149	0 33
2 T C	41	M	2	–	–	23	0 46	Abnormal	560	402	158	0 45
3 C D	43	M	1	–	–	9	0 67	Abnormal	542	419	149	0 40
4 A. E	58	F	0	–	–	6	0 71	Normal	528	378	150	0 46
5 E E	55	M	1	–	D	4	0 69	Abnormal	523	386	137	0 43
6 M F	42	F	0	–	–	9	–	–	536	401	13[illegible]	0 38
7 R K	52	M	0	–	–	6	0 85	Normal	536	365	151	0 48
8 G L	52	M	0	+	D	6	–	–	555	388	166	0 57
9 W M	46	M	1	–	–	11	0 38	Abnormal	539	397	143	0 28
10 S M	56	M	0	–	–	8	0 76	Normal	582	410	172	0 51
11 B M	50	M	0	–	P	15	0 81	Normal	566	422	144	0 37
12 B P	55	M	1	–	–	20	0 83	Normal	566	427	138	0 35
13 J R	59	M	0	–	–	18	0 54	Abnormal	484	391	92	0 24
14 A S	66	M	0	–	–	23	0 74	Normal	535	423	112	0 26
15 C T	56	F	0	–	–	9	0 68	Abnormal	550	407	143	0 40
16 J C	47	M	2	–	–	4	0 73	Normal	569	406	163	0 49
17 S D	46	F	1	–	–	–	–	–	602	441	161	0 42
18 J F	49	M	0	–	–	10	0 74	Normal	514	392	122	0 34
19 R F	55	M	1	–	–	14	0 82	Abnormal	516	403	113	0 29
20 C J	50	M	1	–	–	16	0 91	Normal	526	383	142	0 45
21 J M	46	M	0	–	–	15	0 89	Normal	564	405	159	0 45
22 C M	43	M	1	–	–	6	0 45	Abnormal	523	387	134	0 40
23 H N	52	M	1	–	–	5	0 32	Abnormal	550	387	163	0 54
24 R N	59	M	0	–	–	6	0 80	Normal	562	413	148	0 40
25 E S	54	F	0	–	–	24	0 79	Abnormal	538	405	133	0 35

Meds. = medications P propranolol D digitalis A antiarrhythmic agents

Table 1 Continued

Patient	Clinical					Hemodynamic			STI			
	Age	Sex	Prior AMI	CHF	Meds	LVEDP	LVEF	LVWM	QSI	LVETI	PEPI	PEP/LVET
2 V												
1 K A	51	M	0	+	–	–	–	–	545	391	154	0 49
2 V B	69	M	0	–	–	20	0 89	Normal	522	384	157	0 46
3 L. D	51	M	2	+	D	13	0 63	Abnormal	559	423	136	0 34
4. R E	40	M	0	–	–	6	0 68	Abnormal	548	387	161	0 48
5 G F	46	M	1	–	–	7	0 69	Normal	631	426	153	0 43
6 K. G	44	M	1	–	A	10	0 55	Abnormal	547	393	154	0 46
7 R. C	48	M	0	–	–	22	0 82	Normal	557	431	126	0 31
8 V H	56	F	0	+	D	5	0 96	Normal	536	386	150	0 46
9 N H	49	M	1	–	–	10	0 52	Abnormal	578	454	124	0.29
10 R H	54	M	0	–	–	23	0 68	Abnormal	551	425	126	0 32
11 M H.	63	M	1	+	–	17	0 42	Abnormal	481	352	129	0 46
12 E K	60	F	1	–	–	17	0 75	Normal	540	420	120	0 30
13 W K	60	M	1	+	A D	4	0 80	Normal	538	393	145	0 41
14 C L.	[illegible]8	M	0	–	–	12	0 81	Normal	544	401	143	0 40
15 H. L.	59	M	1	–	P	6	0 86	Normal	555	388	166	0 57
16 R L.	[illegible]7	M	2	–	–	9	0 84	Abnormal	580	442	138	0 34
17 B L.	42	M	3	–	–	6	0 65	Abnormal	560	402	158	0 49
18 T M	62	M	2	–	–	19	–	–	495	371	124	0 38
19 L M	45	M	1	–	–	28	0 25	Abnormal	578	383	195	0 66
20 A M	44	M	0	–	–	16	0 76	Normal	546	389	157	0 52
21 E M	50	M	0	–	–	15	0 89	Normal	508	382	126	0 33
22 D M.	49	M	1	+	D	19	0 23	Abnormal	527	360	167	0 64
23 J M	50	M	1	–	A	8	0 83	Normal	548	370	178	0.59
24 E M	55	F	0	–	–	11	0 68	Abnormal	563	425	138	0 36
25 H [illegible]	49	M	1	–	PA	10	0 61	Abnormal	607	445	136	0 41
26 A. O	48	M	1	–	–	–	–	–	5[illegible]4	405	149	0 40
27 E P	61	F	0	+	DA	1[illegible]	–	–	602	392	10	0 70
28 M S	59	M	1	+	D	[illegible]4	0 15	Abnormal	5[illegible]0	364	186	0 70
29 C W	46	M	0	–	–	[illegible]	–	–	546	403	144	0 42
30 M B	55	F	1	–	–	22	0 49	Abnormal	580	368	149	0 49
31 R G	47	M	2	–	–	15	0 46	Abnormal	561	411	140	0 38
32 W O	50	M	1	–	–	19	0 89	Normal	548	414	134	0 36
33 B S	62	M	0	–	–	0	0 92	Normal	581	423	158	0 42
34 P S	64	F	0	+	–	6	0 47	Abnormal	526	350	174	0 68
35 E W	52	M	2	+	D	27	0 06	Abnormal	518	373	145	0 47

normal or abnormal by the method of Herman and Gorlin [2]

Mean values of systolic time intervals were compared among groups of patients segregated according to the number of coronary arteries obstructed The distribution around the normal range was computed for each STI in patients with and without significant CAD For this analysis the normal range of each interval encompassed one standard deviation around the mean for that interval according to Weissler s regression equations Additionally regression analysis was determined among the following variables (1) individual systolic time intervals (2) number of coronary arteries diseased (3) LVEDP (4) LVEF

Data analysis was performed with the aid of the Olivetti Underwood Programma 101 electric desk computer and the Monroe Electric Programable Statistical Calculator with Student s t test both dependent and independent the chi square analysis and linear regression analysis

Results

Clinical data Of the 113 patients assessed by angiography and STI determination 25 patients

Table I Continued

Patient	Clinical					Hemodynamic			STI			
	Age	Sex	Prior AMI	CHF	Meds	LVFDP	LVEF	LVWM	QS2I	LVETI	PEPI	PEP/LVET
3 V												
1 A A	42	M	0	–	–	–	–	–	584	418	166	0.4[illegible]
2 H A	56	M	1	–	–	8	0.87	Normal	541	390	150	0.46
3 E B	67	M	1	–	–	15	0.55	Abnormal	572	401	171	0.51
4 L B	55	M	0	–	–	8	0.74	Abnormal	547	407	140	0.39
5 E B	58	M	1	–	P	22	0.78	Abnormal	597	425	172	0.4[illegible]
6 A B	54	F	1	–	D	4	0.94	Normal	461	344	117	0.4[illegible]
7 J C	57	M	1	–	–	0	0.50	Abnormal	534	380	154	0.50
8 R D	59	M	2	–	–	14	0.79	Abnormal	515	399	116	0.31
9 R E	68	F	1	+	–	8	0.56	Abnormal	535	399	136	0.3[illegible]
10 M F	65	M	1	+	–	18	–	–	554	393	161	0.46
11 L G	48	M	0	+	D	10	0.63	Abnormal	539	[illegible]	184	0.67
12 J H	46	M	0	–	–	14	0.43	Abnormal	509	378	131	0.41
13 B H	51	M	0	–	P	6	0.56	Abnormal	538	397	141	0.40
14 C J	56	M	1	–	–	15	0.77	Abnormal	543	380	163	0.50
15 I L	65	F	0	–	D	12	0.90	Normal	565	418	147	0.36
16 A M	43	M	1	–	–	13	0.31	Abnormal	569	395	174	0.51
17 R P	43	M	4	–	A	35	0.23	Abnormal	581	424	157	0.43
18 O S	54	M	0	–	–	5	0.76	Normal	554	405	149	0.43
19 K S	53	M	2	–	–	18	0.32	Abnormal	520	376	143	0.44
20 G S	40	M	2	–	–	9	0.63	Abnormal	553	372	181	0.62
21 F S	61	M	2	+	D	38	0.29	Abnormal	547	360	188	0.75
22 I C	57	M	0	–	–	12	0.61	Abnormal	532	399	133	0.38
23 D D	37	M	0	–	P	9	0.82	Normal	541	415	126	0.34
24 J F	55	M	1	+	–	18	0.45	Abnormal	587	405	182	0.52
25 H G	51	M	3	+	AD	32	0.13	Abnormal	531	372	159	0.54
26 I S	50	M	1	–	–	15	0.86	Normal	536	390	150	0.46
27 M T	68	M	3	–	D	25	0.71	Normal	525	361	164	0.63
28 J W	46	M	0	–	–	10	0.77	Normal	552	422	123	0.33

had no coronary artery with more than 70 per cent obstruction, or zero vessel disease (0 V), 25 patients had more than 70 per cent obstruction limited to one vessel (1 V) 35 patients had disease of two coronary arteries (2 V), 28 patients had more than 70 per cent obstruction in all three vessels (3 V) (Table I)

All of the patients suffered from chest pain suggesting ischemic heart disease in 82 per cent, it was the only symptom suggestive of cardiac disease In 18 per cent, however there was clinically apparent congestive heart failure (CHF) as well A greater proportion of patients with 2 V and 3 V disease had concomitant CHF than did those with 0 V and 1 V disease—25 and 8 per cent respectively (Table II) Accordingly, more patients with 2 V and 3 V disease used digitalis preparations and antiarrhythmic agents than did the 0 V and 1 V patients The proportion of patients in each of these two categories receiving propranolol was approximately the same however—10 and 8 per cent, respectively (Table II) The history of prior acute myocardial infarction was increasingly greater with increasing vessel involvement from an incidence of 0.24 per patient with 0 V disease to 1.04 per patient with 3 V disease (Table II) Comparison of the STI in patients with and without prior AMI failed to reveal significant variation (Table III)

Systolic time intervals Significant variation was found in mean PEPI LVETI and PEP/LVET when comparisons were made according to coronary arteries diseased (Table IV) PEPI was significantly greater in both 2 V and 3 V patients than in 0 V patients, LVETI was significantly less in 3 V patients than in 0 V patients the mean PEP/LVET was significantly greater in 3 V patients than in either 0 V or 1 V patients and was also significantly greater in 2 V patients than in 0 V patients (Fig 2) There was no

Table II Clinical data according to number of diseased coronary arteries (70 per cent obstruction)

Patient group	No of patients	Clinical data: Symptoms: Pain only	Pain + CHF	Medications: P	D	A	Prior AMI: No	Incidence†
0 V	25	22 (88%)	3 (12%)	4	3	0	6	0 24
1 V	2[illegible]	24 (96%)	1 (4%)	1	[illegible]	0	14	0 56
2 V	35	25 (72%)	10 (28%)	2	7	5	28	0 80
3 V	28	22 ([illegible]9%)	6 (21%)	3	6	2	29	1 04
Total	113	93 (8[illegible]%)	20 (18%)	10	18	7	77	0 68

P propranolol D digitalis A, antiarrhythmi agents.
†Incidence calculated as no of infarcts/no of pati nts in each group

Table III Effect of prior myocardial infarction and abnormal wall motion on systolic time intervals

	Patient No	PEPI (msec)	LVETI (msec)	PEP/LVET
Prior AMI group				
None	58	143 ± 21	402 ± 19	0 41 ± 0 10
One or more	55	149 ± 21	397 ± 25	0 45 ± 0 11
		NS*	NS	NS
LVWM				
Normal	47	140 ± 18	405 ± 21	0 39 ± 0 08
Abnormal	49	150 ± 23	394 ± 25	0 45 ± 0 1[illegible]
		p < 0 05	p < 0 05	p < 0 05

NS = not significant by independ t t test.

Table IV Systolic time intervals and severity of coronary artery disease

Patient group	Patient No	Systolic time interval data (mean ± 1 S D): Q S₂I (msec)	PEPI (msec)	LVETI (msec)	PEP/LVET
0 V	25	544 ± 1[illegible]	136 ± 21	408 ± 20	0 37 ± 0 08
1 V	25	544 ± 2[illegible]	143 ± 19	401 ± 17	0 40 ± 0 08
2 V	35	547 ± 29	148 ± 21	397 ± 28	0 45 ± 0 12†
3 V	28	544 ± 27	1[illegible]3 ± 21†	391 ± 21	0 47 ± 0 10‡

p < 0 05 compared with 0 V by independ t t test
†p < 0 01 compared with 0 V
‡p < 0 01 compared with 1 V

significant variation in mean Q S_2I among 0 V 1 V 2 V or 3 V patients

When data were analyzed according to presence or absence of clinically apparent congestive heart failure there were no significant difference in mean values In addition the significant STI variations among patient groups remained unchanged when CHF patients were excluded from analysis

Comparison of STI between those with and without significant coronary artery disease (0 V vs 1 V 2 V and 3 V grouped together) showed that 8 per cent of 0 V patients had a less than normal Q S_2I whereas 25 per cent of CAD

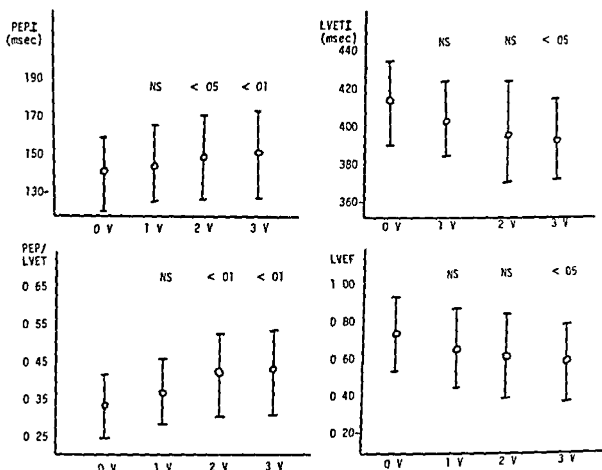


Fig 2 Mean systolic time intervals and left ventricular ejection fraction according to severity of coronary artery disease Significantly longer PEPI in patients with two and three-vessel disease compared to patients without vessel obstruction Significantly shorter LVETI in patients with three vessel disease than in patients without vessel disease Significantly greater PEP/LVET in patients with two and three vessel disease compared with patients without vessel disease

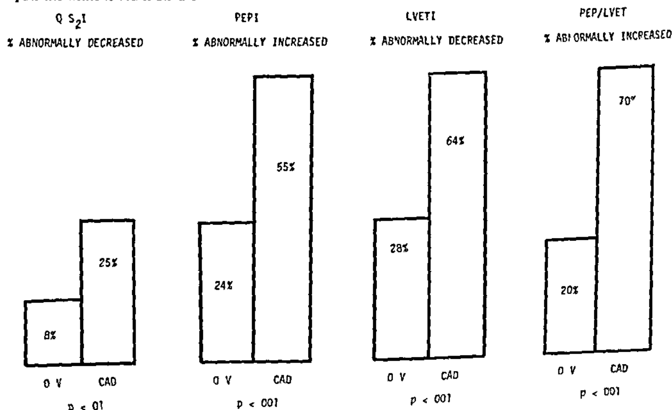


Fig 3 Percentage of patients with abnormal systolic time intervals presence vs absence of significant coronary artery disase (70 per cent vessel occlusion) Patients with coronary artery disease demonstrated more abnormal distributions of systolic time intervals than did patients without coronary artery disease

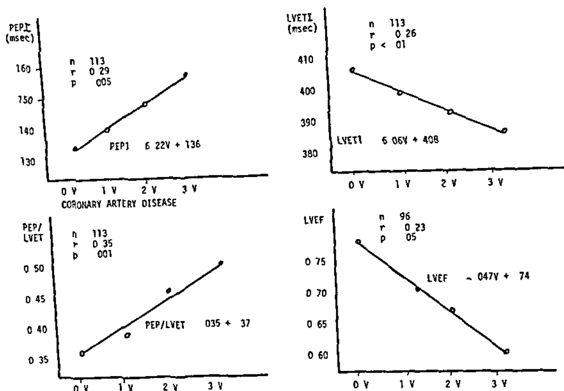


Fig 4 Correlation of systolic time intervals and left ventricular ejection fraction with severity of coronary artery disease Direct correlation was significant for PEPI and PEP/LVET with severity of coronary artery disease Inverse correlation was significant for LVETI and LVEF with severity of coronary artery disease In each of these correlations however the correlation coefficient was low indicative of extensive scattering of individual values.

Table V Angiographic and hemodynamic data according to severity of coronary artery disease

Patient group	*No*	*LVEDP (mm Hg)*	*Number*	*LVEF*	*LVWM (% abnormal)*
0 V	23	11 ± 5	18	0 76 ± 0 17	18
1 V	24	12 ± 8	22	0 68 ± 0 19	50†
2 V	33	14 ± 7	30	0 64 ± 0 24	58†
3 V	27	15 ± 9	26	0 61 ± 0 22	69†

± 1 standard deviation
†$p < 0.01$ compared with 0 V by chi-square analysis.

patients had a less than normal Q S_2I (Fig 3) Twenty four per cent of 0 V patients had a greater than normal PEPI whereas 55 per cent of CAD patients had an increased PEPI Twenty eight per cent of 0 V patients had a less than normal LVETI whereas 64 per cent of CAD patients had a decreased LVETI Twenty per cent of 0 V patients had an increased PEP/LVET as did 70 per cent of CAD patients Each of these differences was significant

Regression analysis showed significant direct correlations between the number of diseased vessels and PEPI and PEP/LVET and significant inverse correlation between the number of diseased vessels and LVETI (Fig 4) No correlation was found between the number of diseased vessels and Q S_2I

Hemodynamic data Of the 113 patients 107 had LVEDP determinations and 96 had left ventriculograms of sufficient quality to allow analysis of LVEF and LVWM and these data were analyzed for correlation with severity of coronary artery disease (Table V) The mean LVEDP did not vary significantly with the number of diseased vessels but the mean LVEF was found to decrease significantly from 0 V to

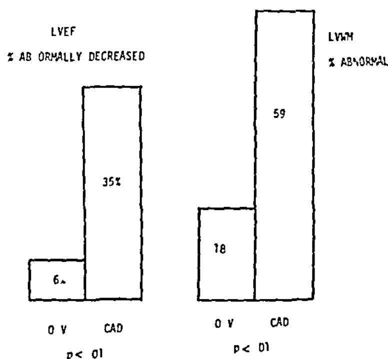


Fig 5 Percentage of patients with abnormal left ventricular ejection fraction and left ventricular wall motion presence vs absence of coronary artery disease Patients with coronary artery disease demonstrated more abnormal distributions of ejection fraction and wall motion than did patients without coronary artery disease

3 V patients (Fig 2) The distributions for LVEDP LVEF, and LVWM were compared between the 0 V and CAD patients (Fig 5) The LVEDP distribution did not show significant variation, however, 6 per cent of 0 V patients had a lower than normal LVEF whereas 35 per cent of CAD patients had a low LVEF, and only 18 per cent of 0 V patients had abnormal LVWM, whereas 59 per cent of CAD patients had abnormal LVWM Significant correlation by regression analysis was noted between the number of vessel involved and LVEF but not LVEDP (Fig 4) In addition, the LVEF correlated directly with LVETI and inversely with PEPI and PEP/LVET (Fig 6)

Patients with normal LVWM had significantly greater mean LVETI and significantly smaller mean PEPI and PEP/LVET than did those patients with abnormal LVWM (Table III)

Discussion

Systolic time intervals are reliable indicators of left ventricular function showing characteristic changes in diminished left ventricular performance elongated PEP and shortened LVET, with resultant increased PEP/LVET [8] Thus the ratio PEP/LVET is the most sensitive indicator of left ventricular dysfunction The PEP and LVET are also reliable though slightly less sensitive That these changes were seen in the patients in this study suggests that this process of diminished left ventricular function occurs in the myocardium of patients with coronary artery disease

Furthermore the greater abnormalities of STI with increasing coronary artery involvement suggest a progressive worsening of myocardial performance with increasing severity of coronary artery disease This was supported by the hemodynamic and clinical data The more severe the coronary artery disease, the lower was the left ventricular ejection fraction and the greater the incidence of abnormal left ventricular wall motion Furthermore a greater proportion of patients with abnormal wall motion had abnormal mean systolic time intervals than patients with normal wall motion Similarly the more severe the coronary artery disease, the greater the incidence of prior myocardial infarction and congestive heart failure The group of patients with prior infarction had no significantly different mean systolic time intervals compared with the noninfarction group and the observed changes in the systolic time intervals between groups remained unaltered with the exclusion of the patients with heart failure, thus showing that the presence of overt heart failure was not responsible for the observed STI variations between groups It has been shown that clinically apparent heart failure occurs in 17 to 45 per cent of all patients with CAD and that this incidence

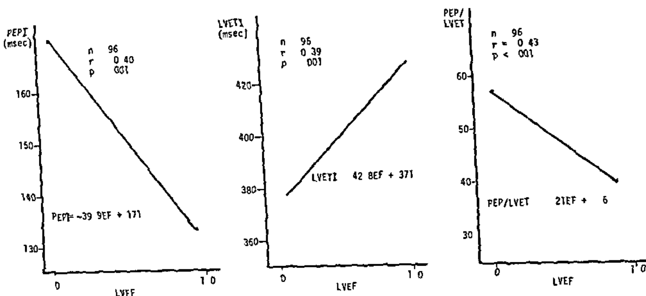


Fig 6 Correlation of systolic time intervals with left ventricular ejection fraction Inverse correlation was significant for PEPI and PEP/LVET with LVF and direct correlation was significant for LVETI with LVEF The correlation coefficient however was low for each correlation indicative of extensive scattering of individual values

bears a rough relationship to the severity and extent of the underlying vessel disease[22] The results of this study suggest that although overt heart failure is more evident with increasing CAD underlying left ventricular dysfunction is more pronounced in a parallel manner even without overt CHF

That the observed changes in systolic time intervals correlate with normal or abnormal left ventricular wall motion and ejection fraction more than with incidence of heart failure or prior infarction can be explained by the more objective indication of left ventricular dysfunction provided by the former The functional abnormality may reflect variably impaired left ventricular myocardial contractility resulting from dynamic changes in degree of ischemia in addition to the development of noncontractile myocardial segments[5] Our studies however did not demonstrate the excellent inverse correlation between PEP/LVET ratio and ejection fraction previously demonstrated by Weissler and others[9]

The poor correlation between systolic time intervals and number of coronary arteries involved emphasizes the importance of the relation between the degree of coronary artery disease and ventricular performance since severe disease may be associated with good performance if the metabolic requirements to the muscle are met.

In summary these data indicate that externally determined systolic time intervals reflect abnormalities in left ventricular performance which in turn appear more pronounced with increasing severity of CAD The correlation between this measurement of ventricular performance and severity of CAD is quite low however This may reflect the ability of even a severely diseased coronary vessel to provide adequate flow with the patient at rest

Summary

Determination of left ventricular performance by external STI was evaluated in 113 patients with possible coronary artery disease undergoing selective coronary arteriography and left ventriculography Angiographically determined significant coronary artery disease was considered as 70 per cent obstruction of a coronary vessel PEPI and PEP/LVET increased with increasing severity of coronary artery disease LVETI decreased with increasing coronary artery involvement Presence of prior myocardial infarction or clinically apparent congestive heart failure did not significantly alter mean STI values when groups were compared according to severity of coronary artery disease LVETI was significantly less for patients with three vessel coronary artery disease than for those with no significant disease PEPI and PEP/LVET were significantly greater in

those with two or three vessel disease than in those without significant disease

Angiographically determined LVEF correlated directly with LVETI and inversely with PEPI and PEP/LVET Abnormal left ventricular wall motion was associated with decreased LVETI and increased PEPI and PEP/LVET LVEDP was not significantly different in any of the groups

These findings indicate that externally determined systolic time intervals reflect abnormalities in left ventricular performance which in turn appear more pronounced with increasingly extensive coronary artery disease

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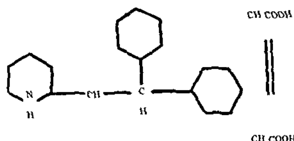
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Clinical evaluation of perhexiline maleate in the treatment of patients with chronic coronary insufficiency

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Perhexiline maleate (Pexid) a new compound synthesized by the Wm S Merrell Laboratories Cincinnati Ohio U S A has been clinically investigated to determine its effectiveness in the relief of angina pectoris

The structural formula of perhexiline is the following



The pharmacologic effects of perhexiline as described in several studies can be summarized as follows (1) Coronary and systemic vasodilation are not reduced in dogs pretreated with propranolol hexamethonium atropine reserpine and dibenamine (2) There is a negative chronotropic effect both on the heart of the intact dog and on isolated guinea pig and rat atrial muscle (quinidine like action) (3) There is reduction of left ventricular work fall in oxygen consumption and increase in cardiac efficiency in dogs with right heart bypass (4) A diuretic action of perhexiline was evidenced in the rat [8] in the dog [7] and in man (5) Feinsilver Aviado and Cho[9] demonstrated a bronchodilator action of perhexiline in dogs and man

Some preclinical trials in healthy volunteers showed after oral administration of perhexiline a decrease in exercise induced tachycardia [9, 11] In other studies carried out in patients with coronary heart disease perhexiline raised the threshold of pacing induced angina pectoris and enhanced correlated extraction of lactate and oxygen Furthermore in these same patients the drug under study improved left ventricular function—i e there was an increase of SWI/LVFP (Stroke work index/left ventricular filling pressure) after exercise on a bicycle ergometer [1 1]

Perhexiline was studied by single intravenous administration[13] to patients with coronary artery disease The drug decreases heart rate and oxygen consumption and in some cases increases coronary blood flow

The biological half life of the drug in man ranges from 3 to 12 days [8] showing remarkable individual variations

Clinical trials carried out in the United States of America Brazil Great Britain and Italy consistently showed that the oral administration of perhexiline is effective in bringing about a reduction of both the number of crises and of NTG (nitroglycerin) consumption in patients with coronary insufficiency [7]

The antiarrhythmic activity of perhexiline was assessed in patients with coronary insufficiency exhibiting ventricular arrhythmia and studied with dynamic electrocardiography [3, 33]

The incidence of side effects under perhexiline treatment has varied from negligible[17, 1, 23] to

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Table I Basic data

Admission No and patient s initials	Age (yr)	Sex	Duration of angina (yr + ms)
1 P G	64	M	2+4
2 R G	66	M	2+4
3 M L	54	M	1+2
4 M C	51	M	1+2
5 P L	58	M	1+2
6 B M	55	M	> 4
7 Z A	64	F	> 4
8 T T	49	M	> 4
9 G A	58	M	2+4
10 C E	65	M	< 1
11 G G	61	F	> 4
12 F G	63	M	> 4
13 T G	50	M	2+4
	Mean 58 3	F = 15 4% M = 84 6%	

Table II Duration of perhexiline treatment in 13 patients admitted to the study

Admission No	Duration of treatment (ms)
1	11 4
2	12.5
3	10 5
4	27 7
5	27 0
6	27 4
7	20 9 (– 1 ms)
8	20 6
9	26 8
10	23 4
11	25 2 (– 4 ms)*
12	23 4 (– 2 7 ms)
13	14 0
Mean	20 7†

*Temporary discontinuation of treatment (months)
†Mean values are not inclusive of discontinuation periods

moderate,[21] with dizziness and nausea being the most prominent clinical adverse reaction Laboratory investigations evidenced temporary rises of serum transaminase levels in some patients, but no important abnormalities of other liver function tests were reported [21 3 28 33]

Materials and methods

Perhexiline has been previously investigated in our service in patients with ischemic heart disease This 6 week double blind study, comparing perhexiline with placebo and prenylamine, has been published recently[24] as a part of a multicenter investigation

In order to confirm these results we carried out a long term open trial in similar patients the duration of this study for each patient varied from a minimum of one year to a maximum of more than two years

Patients with coronary heart disease, complaining of angina pectoris at rest and/or after effort, were admitted and the diagnosis of coronary insufficiency was based on anamnestic data and mainly on ischemic ECG alterations

Progressive number of admission to the trial, age sex, weight, and duration of disease for each of the 13 patients are reported in Table I

Only one patient suffered from angina pectoris for less than one year, in all remaining cases anginal symptoms had been present for more than one year

Prior myocardial infarction was reported by three patients Surgical revascularization of the myocardium had been attempted unsuccessfully in one of these subjects 6 months prior to the admission to the present study

Other antianginal medications had been used in all these patients Six of them had taken part in the earlier controlled double blind clinical trial comparing perhexiline, placebo, and prenylamine [24]

In all patients the starting dose of perhexiline was 400 mg daily (200 mg tablets twice a day) This dosage schedule was modified in four patients In two cases an increase in dosage was suggested on the basis of a worsening of symptoms during treatment The dosage was increased to 200 mg three times a day for 2 months in one patient, and for 3 months in the other, conversely, two patients were given a reduced dose (in one case 200 mg once daily for one month and 200 mg every other day for a second month another patient took 200 mg daily in the last 5 months of treatment) During the whole period of treatment all other antianginal drugs but NTG were discontinued The duration of treatment for each patient is reported in Table II

Each patient was given a diary and asked to note daily the number of anginal attacks and of NTG tablets assumed

Before entering the study, in each case the following data were recorded body weight pulse

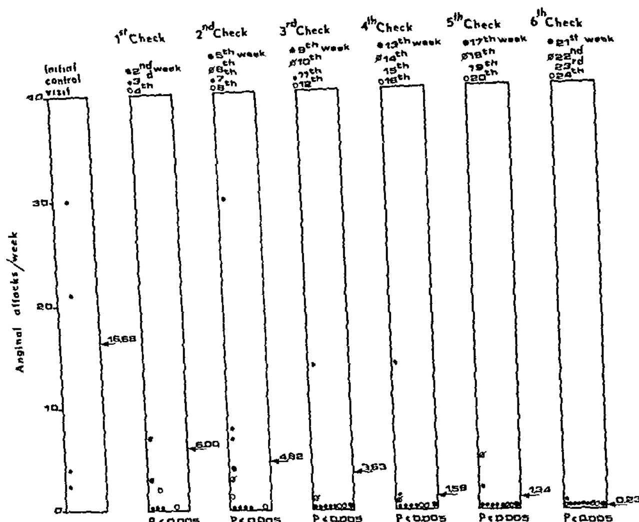


Fig 1 Mean number of weekly angina crises recorded in 11 subjects with angina at rest

rate blood pressure breath rate body temperature number of anginal attacks per week NTG intake per week ECG red blood cells count hemoglobin white blood cell count platelet count prothrombin time blood sugar BUN (blood urea nitrogen) uricemia alkaline phosphatase (U/L) SGOT (mU/ml) SGPT (mU/ml) urine analysis

During the trial the above data were checked at 4 week intervals on an outpatient basis side effects and relevant clinical data were recorded and a resting ECG was carried out

Laboratory control studies were first performed after 4 weeks then after 6 weeks and eventually at 8 week intervals for a total of 17 times in those patients who continued trial for 27 months

Differences between number of anginal crises and NTG consumption before perhexiline treatment and after every control visit have been

Table III Weight recordings

Admission No	*Basal weight (Kg)*	*Final weight (Kg)*	*Changes (Kg)*
1	89	87	−2
2	68	65	−3
3	69	66	−3
4	98	91	−7
5	90	90	0
6	74	63	−9
7	75	63	−12
8	78	77	−1
9	(108)	(90)	(−18)
10	72	67	−5
11	59	64.8	+5.8
12	74	73.5	−0.5
13	69	71.5	+2.5
Mean (without Pt. 9)	76.08 ±3.18	73.23 ±3.06	−2.85 (−3.7%)

Patient was on hypocaloric diet.

Table I Basic data

Admission No and patient s initials	Age (yr)	Sex	Duration of angina (yr + ms)
1 P G	64	M	2+4
2 R G	66	M	2+4
3 M L	54	M	1+2
4 M C	51	M	1+2
5 P L	58	M	1+2
6 B M	55	M	> 4
7 Z A	64	F	> 4
8 T T	49	M	> 4
9 C A	58	M	2+4
10 C E	65	M	< 1
11 G G	61	F	> 4
12 F G	63	M	> 4
13 T G	50	M	2+4
	Mean 58 3	F = 15 4% M = 84 6%	

Table II Duration of perhexiline treatment in 13 patients admitted to the study

Admission No	Duration of treatment (ms)
1	11 4
2	12 5
3	10 5
4	27 7
5	27 0
6	27 4
7	20 9 (– 1 ms)*
8	26 6
9	26 8
10	23 4
11	25 2 (– 4 ms)*
12	23 4 (– 2 7 ms)*
13	14 0
Mean	20 7†

Temporary discontinuation of treatment (months)
†Mean values are not inclusive of discontinuation periods

moderate [21] with dizziness and nausea being the most prominent clinical adverse reaction Laboratory investigations evidenced temporary rises of serum transaminase levels in some patients but no important abnormalities of other liver function tests were reported [21 5 26 33]

Materials and methods

Perhexiline has been previously investigated in our service in patients with ischemic heart disease This 6 week double blind study, comparing perhexiline with placebo and prenylamine has been published recently[24] as a part of a multicenter investigation

In order to confirm these results we carried out a long term open trial in similar patients, the duration of this study for each patient varied from a minimum of one year to a maximum of more than two years

Patients with coronary heart disease, complaining of angina pectoris at rest and/or after effort were admitted and the diagnosis of coronary insufficiency was based on anamnestic data and mainly on ischemic ECG alterations

Progressive number of admission to the trial age sex, weight and duration of disease for each of the 13 patients are reported in Table I

Only one patient suffered from angina pectoris for less than one year, in all remaining cases anginal symptoms had been present for more than one year

Prior myocardial infarction was reported by three patients Surgical revascularization of the myocardium had been attempted unsuccessfully in one of these subjects 6 months prior to the admission to the present study

Other antianginal medications had been used in all these patients Six of them had taken part in the earlier controlled double blind clinical trial comparing perhexiline, placebo and prenylamine [24]

In all patients, the starting dose of perhexiline was 400 mg daily (200 mg tablets twice a day) This dosage schedule was modified in four patients In two cases an increase in dosage was suggested on the basis of a worsening of symptoms during treatment The dosage was increased to 200 mg three times a day for 2 months in one patient and for 3 months in the other conversely, two patients were given a reduced dose (in one case 200 mg once daily for one month and 200 mg every other day for a second month another patient took 200 mg daily in the last 5 months of treatment) During the whole period of treatment all other antianginal drugs but NTG were discontinued The duration of treatment for each patient is reported in Table II

Each patient was given a diary and asked to note daily the number of anginal attacks and of NTG tablets assumed

Before entering the study in each case the following data were recorded body weight pulse

Table IV Side effects

Admission No	*Gastric pain*	*Dizziness*	*Unsteadiness*	*Nausea*	*Vomiting*	*Asthenia*	*Paresthesias*
1	–	10 times (wks 3 to 38)	–	1 time (wk 7)	–	–	–
3	–	–	–	2 times (wks 42 and 46)	1 time (wk 46)	–	–
4	–	1 time (wk 15)	–	–	–	–	–
7	2 times (wks 71 and 91)	1 time (wk 11)	–	–	–	3 times (wks 15 64 and 67)	1 time (wk 11)
8	–	–	–	–	–	1 time (wk 23)	–
10	–	–	–	–	–	5 times (wks. 60 to 100)	–
11	–	3 times (wks 11 to 16)	1 time (wk. 12)	–	–	1 time (wk 4)	–

Table Va Transaminase serum levels grouped data for patients under perhexiline treatment

SGOT (mU/ml)	*Patients* No	*Patients* %	SGPT (mU/ml)	*Patients* No	*Patients* %
50	9	69 2	35	7	53 8
50 100	3	23 1	35 100	4	30 8
100	1	7 7	100	2	15 4

Table Vb Transaminase serum levels Onset time of abnormal values (SGOT ≥ 50 mU per milliliter SGPT ≥ 35 mU per milliliter

SGOT		SGPT	
Admission No	*Weeks of perhexiline treatment*	*Admission No*	*Weeks of perhexiline treatment*
6	67	1	23
		4	80
7	30	6	67
11	24	7	30
		9	15
1	15	11	16

72 9 per cent in NTG consumption as compared with basal values was seen NTG consumption practically had ceased at the sixth checkup (reduction up to 99 8 per cent as compared with basal value)

Other clinical findings No important changes were recorded in pulse rate at rest blood pressure breath rate and body temperature

Body weight changes occurred throughout the trial in all 13 patients treated with perhexiline as summarized in Table III

ECG findings A definite improvement of the ST segment was recorded in 10 patients treated with perhexiline (76 9 per cent)

In nine subjects (69 2 per cent) we observed a prolongation of the Q T interval a large U wave and sometimes a biphasic T wave without serum potassium changes These ECG features in our experience are more evident under treatment with lidoflazine amiodarone and prenylamine

Side effects

Subjective Table IV is a summary of side effects observed in seven patients being treated with perhexiline

Laboratory investigations Tests of hematological and renal function remained normal

Changes in serum transaminases (SGOT and/or SGPT) however did occur in six patients but generally appeared after some months of therapy Data are summarized in Tables Va and Vb

One patient showed slightly altered SGOT and SGPT prior to treatment In these six patients serum transaminase levels reverted to normality after discontinuation of drug (five cases) or spontaneously while treatment was being maintained (one case) After discontinuation perhexiline treatment was restarted in two out of five cases and no changes in SGPT and/or SGOT were observed throughout the second treatment periods of 41 and 54 weeks respectively

Changes in alkaline phosphatase were recorded in one case but altered values normalized within the fiftieth week of treatment Table VI summarizes values for each patient

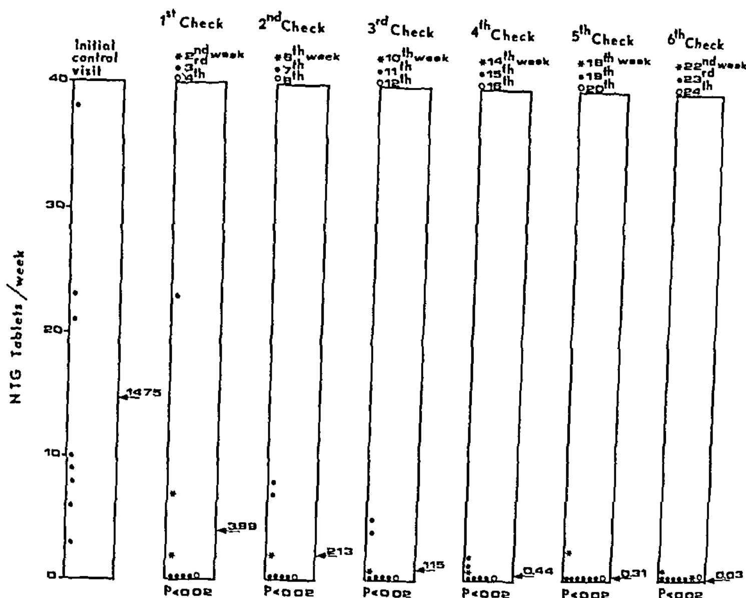


Fig 2 NTG consumption per week in 11 patients with angina at rest before and during perhexiline treatment

statistically evaluated by means of the Wilcoxon test [31]

Results

Angina attacks and NTG consumption Two of the 13 patients are considered separately as their angina almost exclusively presented after effort, with a variable number of anginal crises per week Only one of these two subjects usually took a maximum of 8 to 10 NTG tablets per week In both cases symptoms of angina pectoris definitively disappeared within 4 to 8 weeks from the initiation of perhexiline therapy

The data on the mean number of weekly angina crises recorded in the 11 remaining subjects with angina at rest are presented in Fig 1 The average basal value of angina attacks per week was 16 7, the reduction of crises with perhexiline treatment exceeded 60 per cent at the first control visit and 98 per cent at the sixth checkup as compared with mean basal value These reductions are statistically significant Therapeutic results at the sixth checkup were maintained throughout the remaining treatment period, in one case they lasted 4 weeks after discontinuation of treatment

In six of the 11 patients a satisfactory reduction of anginal crises (75 per cent) was achieved within 3 to 4 weeks in the remaining five subjects from 5 to 23 weeks were needed to achieve the same result

Only eight out of 11 patients with angina at rest usually took NTG tablets to abort acute anginal attacks Fig 2 shows NTG consumption per week in this group before and during perhexiline treatment The mean basal value of NTG tablets per week was 15 7 At first control visit a reduction of

three times the average weight loss observed by Lyon and associates[9] in 8 weeks of treatment These authors ascribe weight loss to the diuretic activity of the drug We were unable to confirm this hypothesis although Czerwinski and associates[8] observed in man a limited but significant increase of diuresis

Seven patients reported subjective side effects but only one patient with peptic ulcer discontinued treatment because of nausea and vomiting The most frequent adverse effect dizziness was reported by four patients but two of these complained of the same reactions while receiving placebo in the course of a previous double blind investigation On the other hand dizziness occurred also in patients treated with other antianginal agents In conclusion we agree with Pilcher and associates[26] in defining the subjective side effects as clinically unimportant in view of the prolonged duration of the treatment

With regard to the serum transaminase increase under perhexiline treatment a literature review showed some discrepancies In some short term studies perhexiline administered in a dosage of 400 mg per day for 4 to 8 weeks did not cause changes in serum transaminase levels[20 24 2] but Burns Cox and associates[11] reported slightly raised SGOT levels in some patients treated for 4 to 8 weeks with perhexiline 200 mg twice daily Hirshleifer[1] in a long term study did not observe any increase in transaminase levels in patients treated for 18 months with perhexiline whereas Pilcher and associates[26] Garson Gulin and Phear[2] and Gitlin[27] in their long term studies (6 to 32 months) with doses varying from 100 to 600 mg daily found significant increases in serum transaminase levels in varying percentages of their respective series

Rees[3] treated 16 patients with perhexiline for more than a year 10 were receiving 400 mg per day and six were on 200 mg per day In three out of 16 subjects an elevation of SGOT within normal limits was recorded with prompt return to baseline values when the drug was withdrawn Gamma glutamyl transpeptidase levels were normal in patients on 200 mg per day whereas in six of the 10 on 400 mg per day values higher than normal upper limits were observed

In a review of all laboratory findings of short and long term studies Newberne stated that serum enzyme elevations in patients given 300 or 400 mg of perhexiline daily have been relatively mild and transient in nature with little or no tendency to progress suggesting that these functional aberrations have no clinical significance Moreover Van Peenen and Files[4] observed SGOT abnormalities in 16 per cent of hypertensive patients under chronic treatment with antihypertensive agents

In our study 6 out of 13 patients showed elevation of transaminase levels without other signs of liver impairment In our observations a long delay seems to occur prior to the onset of these enzymatic aberrations In all cases return to normal values was recorded after discontinuation of drug or even with continued therapy

/In the present investigation no death or case of acute myocardial infarction occurred under perhexiline treatment Only one patient underwent surgical treatment of coronary artery disease without benefit 6 months before entering the present study

In conclusion our results are encouraging but further investigations in larger series of patients are advisable in order to confirm whether perhexiline improves survival of patients with angina pectoris or changes the natural history of coronary artery disease ✓

We are indebted to S Merrell Laboratories for supplying perhexiline maleate (Pexid)

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Table VI Alkaline phosphatase

Admission No	Age (yr)	Sex	Normal limits (U/L)	Basal value (U/L)	Max value (U/L)	Week	Final value (U/L)
1	64	M	21 79	28	38	42	38
2	66	M	21 79	26	37	23	18
3	54	M	18 75	52	72	36	70
4	51	M	18 75	36	62	27	47
5	58	M	18 75	25	60	23	24
6	52	M	18-75	68	80	21	39
7	64	F	20-79	60	148	42	46
8	49	M	20-77	50	50	3	34
9	58	M	18-75	23	48	65	42
10	65	M	21 79	70	71	30	48
11	61	F	20-79	20	30	64	24
12	63	M	21 79	42	60	95	48
13	50	M	18-75	15	28	24	18

Table VII Studies on perhexiline long term therapy

Authors and date	No of patients	Dosage schedule (mg/day)	Duration (ms)
Hirshleifer 1969	13	150-500	2 18
Martins de Oliveira et al [31] 1973	34	400	18
Garson et al [32] 1973	46	100-400	6 11
Pilcher et al 1973	46	400-600	11 3 (mean) 32 (max)
Gitlin * 1973	22	400	6
Rees 1973	16	200-400	>12(mean)
Masoni et al (present study)	13	400	20 7 (mean) 27(max)

* With propranolol.

Discussion

Some long term studies (see Table VII) demonstrated that the beneficial effect of perhexiline, already shown in short term studies,[18 19 21 24] is maintained in long term therapy

In the present study the mean duration of the treatment (20 7 months) is among the longest reported in the literature Our data on the therapeutic efficacy of perhexiline are in agreement with those reported by previous authors [25 27 35] On the other hand, our results are far more satisfactory than those reported by Zeft and Amsterdam and their colleagues[36 37] with propranolol

It is widely accepted that angina pectoris results from an imbalance between myocardial metabolic requirements and oxygen supply [38] Several factors can originate such imbalance the main one being an increase in the work of the heart and a reduction in coronary blood flow Systolic blood pressure and heart rate are important determinants of myocardial oxygen consumption [39] Onset of angina, according to Robinson,[40] was consistently related to the product of systolic blood pressure and heart rate On the other hand, perhexiline s effectiveness in reducing tachycardia after effort has been widely demonstrated in healthy volunteers[10 11] and has been confirmed in subjects with angina pectoris [12 13 18 22]

Pepine, Schang and Bemiller[13] suggested that the antianginal activity of perhexiline is related to a better perfusion of ischemic zones

Furthermore, perhexiline s tendency to improve left ventricular functions (increase of SWI/LVFP) should be noted In other words, perhexiline appears to have the beneficial actions of both NTG and propranolol without their undesirable effects [12]

In our trial Perhexiline did not influence heart rate at rest and this result is confirmed in the literature [10 21] The administration of perhexiline was followed by slowing of the heart rate in animals as a consequence of a prolongation of depolarization and repolarization times both of the atrial muscle and of the sinoatrial node [5] This quinidine like action does not reduce myocardial contractile activity and could explain ECG features observed in patients under treatment

No blood pressure variations have been observed and this is in agreement with data reported in the literature [12 19]

In our patients a mean weight loss of 2 85 kilograms per patient has been observed This is

Atherosclerotic ulcerative disease and associated aneurysms of the coronary arteries

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There are many variations in the atheromatous process as it affects the coronary arteries of man and these have been well described pathologically. We have become increasingly aware of a group of subjects who, on coronary arteriography, are found to have apparent ulceration of atheromata resulting in dilation of localized segments of the coronary arteries with clear localized single or multiple aneurysms in some cases. An extensive literature review presents 45 such atherosclerotic aneurysms and states that up to that time no case had been diagnosed antemortem. The present report is a retrospective study to determine whether those subjects with the angiographic lesion demonstrated during life have a recognizable clinical entity and whether standard therapeutic measures are appropriate.

Methods

Coronary arteriograms are done by the Sones technique through the right brachial artery. Precurved catheters[1] are used if the coronary arteries are not entered well enough with conventional catheters to produce good coronary arterial opacification. This is especially important if the aorta is dilated, unusually tortuous, or associated with brachiocephalic elongation and tortuosity.

All coronary filming is done during nitrite dilation exposing 60 frames per second. The long axis of the patient is recorded perpendicular to the film, thus utilizing the long axis of the frame providing about 75 per cent greater filming area. A seven inch cesium iodide intensifier tube is used currently but was not available in the earlier studies reported here. Only good quality films were accepted in the study.

A running list of the interesting and/or unusual coronary arterial lesions kept in the cardiovascular laboratory was searched for coronary aneurysms and the films reviewed. The catheterization reports of 1,342 other coronary arteriograms were then reviewed for descriptions of coronary arterial ulcerations, dilations, or lesions which would currently be designated as coronary arterial aneurysms. By this means films on 77 patients were selected for careful review. It quickly became apparent that there was a continuous spectrum of lesions from shallow atheromatous ulceration in a localized area to a diffuse ulcerative process involving ever increasing areas of the coronary tree and from questionable dilations to clearly recognizable localized aneurysms (Figs. 1 and 2). Two criteria for a coronary atherosclerotic aneurysm were set. First, readily recognizable atheromatous coronary disease must be present to establish the likelihood of an atherosclerotic origin, and second the localized dilation in the coronary artery must be clearly larger than the artery was presumed to have been as judged by its size above and below the lesion. Thus 15 subjects with severe atheromatous ulceration were selected for detailed study and of these five were arbitrarily stated by both authors to have at least one coronary aneurysm. The aneurysms were measured from the image on the Tage Arno projector and their size estimated by triangulation from the known size of the cardiac catheter

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Table I Clinical data are presented on the 10 patients with ulcerative coronary atherosclerosis and the 5 patients with coronary artery aneurysms (See text)

Patient	Age (yrs)	Height (inches)	Weight (pounds)	Blood pressure (S/D)	Glucose (mg / ml)	Lipid profile (type)	Cholesterol	Triglycerides	Coronary artery aneurysm	Left ventricular status	Systolic/ LVED	Clinical data
1	49	65	120	95/70	79	II	388	112		Antero apical aneurysm	105/40	Aortic aneurysm atypical angina
2	53	67	1 8	165/90	86	Norm	184	46		Good LV contraction	187/14	Angina
3	58	69	143	175/95	64	–	160	10		Good LV contraction	180/34	Atypical angina
4	51	64	117	1?4/95	8	–	?81	157		Good LV contraction	117/14	Myocardial infarction
5	54	66	135	116/80	93	III	343	312		Poor LV contraction	–	Myocardial infarction
6	50	66	166	175/95	97	–	257	148		Fair LV contraction	191/44	Aortic and mitral insufficiency aortic aneurysm
7	49	69	171	140/100†	60	II	386	382	Aneurysm circumflex	Antero apical aneurysm	147/10	Atypical angina
8	60	67	160	13?/76	148	Norm	252	102		Good LV contraction	107/9	Tachy arrhythmia and pain
9	62	68	145	100/80	?0	II A	334	114	LAD aneurysm	Antero apical aneurysm	113/24	Myocardial infarction mild CHF
10	38	69	214	110/80	130	II A	361	137	LAD aneurysm	Very poor LV contraction	138/?1	Myocardial infarction
11	63	69	173	130/80	102	–	296		LAD aneurysm	Antero apical aneurysm	1?8/20	Angina 1971 myocardial infarction 1961
1?	60	68	13?	166/100	100	Norm	100	100		Fair LV contraction	180/17	Abdominal aneurysm angina
13	5?	67	16?	165/70	90	IV	230	140	Small LAD aneurysm	Fair LV contraction	160/23	Myocardial infarction
14	63	71	196	148/104	185	–	245			Poor LV contraction	124/22	Atypical angina
15	38	68	1?0	145/95		IV					–	Myocardial infarction

Hypertensive prior to first myocardial infarction.
†Known hypertensive
S/D Systolic/diastolic
LAD Left anterior descending
LV left ventricular
LVED left ventricular end diastolic
CHF congestive heart failure



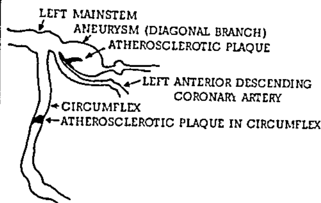


Fig 1 This is a single frame from a left coronary arteriogram with the patient rotated in 30 of right anterior oblique and a diagram of the frame A clear atherosclerotic obstructive lesion is present in the circumflex coronary artery In the diagonal branch of the left anterior descending there is a large aneurysm which has an atherosclerotic plaque tipped up into it from the inferior or cardiac surface The lumen of the aneurysm is clearly considerably greater than that of the vessel from which it arises and the typical associated lesions give strong reason to suspect that the underlying process is atherosclerosis

The clinical records of all 15 patients were then reviewed in detail to make up the present re port

Results

The fifteen patients ranged in age from 38 to 63 years and all were male There was no evident correlation with the risk factors of diabetes or smoking Seven of fifteen patients showed specific lipoprotein abnormalities (see chart) Ten of the patients were overweight with five 20 pounds or more above their ideal weight as determined from standard tables of height and weight [5] Fifty three per cent (8 of 15) were hypertensive (systolic above 140 or diastolic above 90 mm Hg) at the time of the study Of the remaining seven patients, five had a poorly functioning left ventricle and may have been hypertensive prior to this evaluation Indeed historically two of these latter five patients had been on hyperten sive therapy for a varying time in the past but now were not

The presenting signs and symptoms varied (Table I) Only three were evaluated for classical anginal pectoris Four patients had atypical angina which lasted from 1/2 hour to five hours and six patients were seen after myocardial infarction One had a refractory tachyarrhythmia and one had mitral insufficiency

Angiography demonstrated severe diffuse atherosclerosis of the left anterior descending (LAD) right (RCA), and circumflex (CIRC) coronary arteries in 10 out of 15 patients The RCA and LAD together were involved in 14 out of 15 the CIRC was diffusely diseased in 10 out of 15 There were no hemodynamically significant left main stem lesions The LAD was totally occluded in three and the CIRC was occluded in two cases

Left ventricular aneurysms were found in six patients Two patients had antero apical aneu rysms even though the LAD was open to the apex Left ventricular contraction on angiog raphy was considered poor in eight, fair in three and good in four patients None of the latter four had three vessel involvement

There were five subjects with aneurysm of the coronary artery One patient had three aneu rysms one on each coronary artery but each of the others had only one aneurysm There were three aneurysms on the LAD three on the circumflex and one on the right coronary artery Aneurysms varied in size from 4 by 5 mm to 15 by 8 mm with average longitudinal dimension of 8 mm and the dimension perpendicular to the vessel of 6 mm Those on the LAD were the largest Three of these five patients had a left ventricular aneurysm and all demonstrated poor left ventricular contraction on angiography Two subjects had an abdominal aortic aneurysm but there was minimal clinical evidence of cerebral or peripheral vascular disease, and abdominal aort ography was not done on all subjects

There were five deaths in the group of fifteen

adventitia thus with inadequate support dilation and rupture occur [3] If the intima covering a plaque breaks (Fig 3) the grumous material within may be eroded by the bloodstream and the excavated plaque become the site of aneurysm formation Reduced flow velocity increases later al pressure and especially in hypertensive patients may aggravate aneurysmal dilation Concomitantly grumous material from the atheroma and microthrombi of platelets and fibrin resulting from irregular flow swirling in the aneurysm may embolize the small distal vessels resulting in progressive myocardial ischemic destruction This may explain not only the atypical symptomatology but also the high inci dence of poorly functioning left ventricle

In the process of excavation it is possible that a reoriented plaque dissected from its bed by an undermining stream of blood may turn outward en bloc across the the vessel obstructing its lumen completely (see Fig 3) Parallel processes have been reported from aneurysms and ulcerated plaques in the carotid [7,8] renal [10] and other arter ies and from coronary artery aneurysms of congenital [3] unknown [1] and mycotic origin [6] Ultimately sudden death may be related to a large embolic event arrhythmia or the aneurysm may rupture into the pericardium (Fig 3) [3]

It is apparent that the present group of patients is small and highly selected including only those patients with severe ulcerative atheromatous coronary artery disease It may however illus trate that there are many variations in coronary disease which if characterized may be given more appropriate treatment Our study describes a sub set of patients who are frequently overweight hypertensive males and whose presenting symp toms are atypical usually with a sudden onset frequently experienced at rest but unpredictable in duration and progression and with a proneness to sudden death Angiography identifies the group and defines the underlying process as ulcer ated plaques with varying degrees of stenosis and dilation of the distal vessels including frank but small coronary artery aneurysms Considering similar but better known processes in the carotid and renal arteries rational therapy can be pro posed

Ideally the ulcerative process should be defined early and attempts made to prevent their devel opment into the more severe lesions described in this report Obvious abnormalities such as obesity and hypertension should be treated vigorously and diet should be modified appropriate to the lipoprotein phenotype Recent human pathologic studies have shown platelet aggregates within coronary arteries [17] and animal studies have suggested some protection might be gained by use of agents which decrease platelet stickiness and agglutination [18] Surgery should be considered to prevent emboli from the aneurysm or severely ul cerated plaques by their excision or by bypass as it is done in carotid arteries

Clearly more information is needed to guide therapy Since of necessity the diagnosis is made by angiography it will be discovered only by those who pursue a vigorous and aggressive approach to the management of coronary disease The respon sibility of the forerunner demands accurate observation rigorous definition and accurate description to avoid false direction to those who follow

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Fig 2 The 30 right anterior oblique projection of the left coronary artery of a 38 year old man shows a long irregularly ulcerated lesion of the left anterior descending artery terminating in an atherosclerotic aneurysm A small ulcerated aneurysm is present more distally in the left anterior descending artery in its diagonal branch and in the A V groove branch of the circumflex artery

patients with ulcerative coronary disease One resulted from hepatitis presumably contracted at the time of coronary bypass surgery Four deaths occurred so suddenly and unexpectedly the patient did not reach a hospital for treatment Of the ten surviving patients, two presently do sedentary work four have mild symptoms but do not work while the remainder are severely disabled with intermittent congestive heart failure and require close medical supervision

The treatment of these patients varied Four of the 15, one of whom had an aneurysm underwent surgery for stenotic lesions and there was one death from hepatitis in this group as described above The other three subjects have done well after surgery though one has shown significant progression of disease distal to his grafts Three medically treated survivors are receiving coumadin anticoagulant therapy but it is not possible to evaluate the benefit of this intervention

Discussion

The fundamental process in the majority of patients with ischemic myocardial disease is

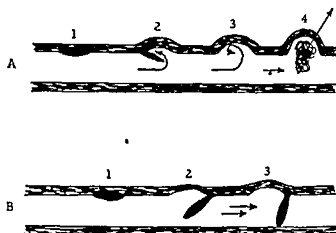


Fig 3 Two possible sequences of coronary atheromatous ulceration are illustrated In *A* the plaque develops a break in its covering intima (1) blood swirls inside the plaque (2) and excavates its grumous content (3) sending microemboli to the periphery Possible terminations are illustrated in (4) Progressive dilation with rupture could occur or thrombosis could result in multiple small fibrin and platelet emboli Larger clots could produce distal embolic occlusion or progressive thrombosis could produce obliteration of the aneurysm and/or the coronary artery In sequence *B* the atheromatous plaque (1) is loosened by an intimal break at its proximal end (2) and the bloodstream undermines the plaque turning it up as a plate which may finally completely occlude the coronary artery (3)

coronary atherosclerosis with intimal thickening and luminal constriction Characteristically during the fifth and sixth decades symptoms from myocardial ischemia appear due to progression of the atheromatous process with progressive coronary constriction intraluminal thrombosis, intramural hematoma, arrhythmia or a combination of these

Most patients in this series did not appear to undergo a steadily progressive disease course Rather, very severe lesions could be found early in the clinical course even in relatively young patients Instead of constricting and occluding lesions in normal sized vessels ulceration dilation, aneurysms and stenotic areas were intermixed Indeed only five patients demonstrated occlusion of a major coronary artery yet ventricular dysfunction was seen in eleven of the fifteen cases It is postulated that the process may be explained by consideration of the ulcerated areas It has been demonstrated that the media adjacent to an intimal plaque becomes thinner with the thickness of the media and intima inversely proportional [6] It is likely that the thin, degenerated media is incapable of normal contraction Furthermore plaques in these thin walled vessels frequently extend through the media into the

Ferrokinetic studies in acute myocardial infarction

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Decreased serum iron is frequently observed in patients with acute myocardial infarction (AMI) Feldthusen and Lassen[1] reported in 1954 a decrease in the serum iron level in patients with AMI who did not have infections as did also Myhrman and Wilander[2] Brucknerova and Pojer[3] and Handjani and associates Bass and Shapira[5] described a series of 122 male and 24 female patients with AMI who displayed hypoferremia The lowest serum iron level measured (47 8 μg/100 ml) was found on the third day after the infarction although in some of the patients a decrease in serum iron was already noticeable the day following the event The serum iron values in these patients returned to their normal levels without any specific treatment at day 9 following the infarction In a control group of 62 patients complaining of chest pains but without myocardial infarction there was no decrease in the serum iron Extension of the infarction or additional pulmonary embolism was accompanied by a further decrease in the serum iron level In most of the series the maximal decrease in the serum iron was noted at day 3 after the infarction

The aim of the present study was to clarify the mechanism of the decrease in serum iron in patients with AMI

Materials and methods

Patients Sixteen patients with AMI and five patients either receiving steroids or suffering from diseases acting as stress factors (the control group) were examined The AMI patients consisted of 12 men in the age range 37 to 70 years (average age 56 8 years) and four 58 to 69 year old women (average age 60 7 years) All patients with AMI were treated with anticoagulants such as heparin administered intravenously immediately after admission to the hospital and coumadin given orally on the subsequent days Five patients had mild diabetes controlled by diet only four had hypertension and one had suffered a cerebrovascular accident prior to admission In one patient polycythemia was detected on admission The diagnosis of AMI was established on the basis of typical clinical and electrocardiographic (ECG) findings as well as the observed increases in serum glutamic oxaloacetic transaminase (SGOT) creatinine phosphate kinase (CPK) and lactic dehydrogenase (LDH) values

The control group consisted of four men 43 to 57 years old (average age 49 2 years) and one 73 year old woman Two were admitted because of severe bronchial asthma treated with steroids two suffered from severe renal colic and one from paroxysmal atrial tachycardia and chest pains but without AMI

Patients having chronic diseases infections bleeding and conditions which could affect the iron metabolism were excluded from the study

Methods Repeated ECG and routine blood examinations were performed in the early morning hours Blood volume was detected by the method of Crispell Porter and Neiset[9] using radioiodinated serum albumin (RISA) with a Picker Hemolitre Detector The normal values are as follows total blood volume 70 ml per kilogram plasma volume 30 ml per kilogram SGOT was examined by the method of Babson and associates[10] (normal values 5 to 30 U) LDH by the method of King and Morris[11] (normal

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Table IV Serum iron total iron binding capacity and iron excretion in urine in patients with AMI and control subjects

	AMI patients					Control subjects day 1
	Day 1	Day 3	Day 9	Day 12	Day 15	
Iron (μg/100 ml)	34 3 ± 19	28 6 ± 15 7	64 9 ± 8.2	90 ± 20 5	98 3 ± 26 8	105 4 ± 22.5
TIBC (μg/100 ml)	33[illegible] ± 4 2	361 ± 45 8	361 ± 34 8	399 ± 55 6	386 ± 35.9	408 ± 69 6
Iron in urine (mg/24 hr)	0 75 ± 0 3				0 71 ± 0 11	0 48 ± 0 13

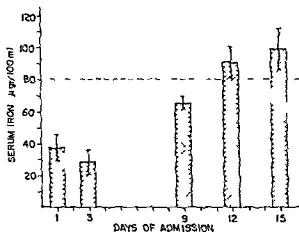


Fig 1 Serum iron levels of patients with AMI at different days after admission The dotted line marks the lower limit of serum iron in controls

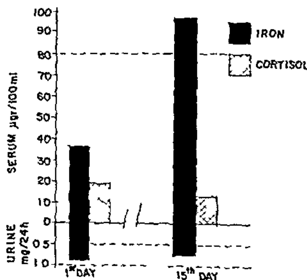


Fig 2 Serum iron and plasma cortisol levels and iron excretion in urine in five patients with AMI The dotted lines mark the lower limit of serum iron and the range of iron excretion in urine in controls

of the patients with AMI and elevated hemoglobin and hematocrit values in one patient all results were within normal limits

In Table II data obtained from the biochemical tests are presented The AMI patients show elevated SGOT and LDH levels Morning plasma 11 OHCS values (Table III) were slightly high in patients with AMI on the day of admission and much higher than the values measured on day 15 in the same patients (54 per cent $p < 0.02$) The night plasma 11 OHCS values were also higher than normal on day 1 and much higher (104 per cent) than the values found on day 15 after admission ($p < 0.01$)

Serum iron iron binding capacity and the 24 hour iron excretion in the urine are shown in Table IV The lowest serum iron values were found at day 3 after the infarction they rise to the lower limit of the normal at day 9 and to within the normal range at day 12 There was a highly significant statistical difference ($p < 0.001$) between the serum iron levels at days 1 and 15 Fig 1 shows serum iron levels on different days after admission in patients with AMI There was no difference in the 24 hour iron excretion in the urine of patients with AMI on days 1 and 15 after admission Fig 2 illustrates the relationship between serum iron plasma 11 OHCS and urine iron excretion It is evident that the difference in serum iron levels on days 1 and 15 does not result from iron loss in the urine The half time ^{59}Fe plasma clearance values of patients with AMI on days 1 and 15 are shown in Fig 3 On day one these values ranged from 45 to 98 minutes (mean 72 ± 15 minutes) that is they were reduced immediately after the event but returned to normal 2 weeks thereafter—in all but one patient with polycythemia where the value remained low The difference between the mean half time ^{59}Fe plasma clearance values on days 1 and 15 was highly significant ($p < 0.001$) There was no relationship between the severity of clinical signs and iron clearance rates The ^{59}Fe

Table I Hematological findings in patients with AMI and control subjects (range and mean values)

	AMI patients					*Control subjects day 1*
	Day 1	*Day 3*	*Day 9*	*Day 12*	*Day 15*	
Hemoglobin (Gm /100 ml)	12 7 18 5 (14 6)	12 1 20 0 (14 4)	13 0 16 2 (14 2)	11 6-15.8 (14 0)	12.2 16 0 (13.8)	13 5 15 1 (14 1)
Hematocrit (%)	39 53 (44.5)	35 57 (44.5)	39-50 (43)	36-47 (42.5)	36-47 (41 5)	41-48 (44)
WBC (/mm)	8 400 18 700 (12 700)	6 300-21 200 (11 600)	7 000-15 800 (9 200)	6 100-14 800 (8 750)	4 800-16 300 (8 900)	6 900-9 000 (7,240)
Platelets (/mm)	150 000-307 000 (220 000)	157 000 440 000 (241 000)	151 000-470 000 (254 000)	145 000-467 000 (292 000)	207 000-380 000 (292 000)	170 000-256 000 (188 400)
Total blood volume (ml /kg)	55 0 87 5 (73 5)				53 5-90 5 (74.5)	64 5 78.3 (73.2)
Plasma volume (ml /kg)	32 5 50 (43 0)				33 0 51 5 (43 0)	38-44 (41 6)
Red cell mass (ml /Kg)	22.5-43 5 (31 2)				22 0-42 5 (31 5)	26-38 (31.2)

Table II Biochemical findings in patients with AMI and control subjects (range and mean values)

	AMI Patients					*Control subjects day 1*
	Day 1	*Day 3*	*Day 9*	*Day 12*	*Day 15*	
SGOT (U)	30 215 (103)	29 116 (64)	20-35 (29)	5 10 (7.8)	12 15 (13)	20-25 (21 4)
LDH (U)	71 570 (252)	50-373 (229)	55 194 (105)	62 117 (82.5)	52 104 (79)	49-86 (65 6)
Total proteins (Gm /100 ml)	6 7 8 0 (7 1)	6.2-8 1 (6 9)	6 2 7 4 (6 9)	6 5 7 6 (7 1)	6 6-7 8 (7 0)	6 6-7 4 (7 1)
Albumin (Gm /100 ml)	3 7 5 2 (4 5)	3 2 4.5 (3 9)	3 4-4 5 (3 9)	3 6-4 1 (3 75)	3 5-4 8 (4 1)	4 1-4.5 (4 3)
Globulin (Gm /100 ml)	2 0-4 2 (2 8)	2 3 3 4 (2 8)	2 4 3 4 (2 9)	2 8 3 9 (3 3)	2 3 3 3 (2 9)	2 5-2 9 (2.7)

Table III Plasma 11 OHCS values in patients with AMI and control subjects

	AMI patients		*Control subjects day 1*
	Day 1	*Day 15*	
Morning (µg/ 100 ml)	24 8 ± 3 0	16 0 ± 4 2	17 5 ± 4 4
Night (µg/100 ml)	15 7 ± 3 0	7 7 ± 2 84	6 2 ± 1 8

values, 30 to 120 U) 11 Hydroxycorticosteroids (11 OHCS) were determined by the method of de Moor and associates[12] (normal morning values 13 to 23 µg/100 ml , evening values 4 to 7 µg/100 ml) Serum iron and total iron binding capacity were determined by the methods of Trinder[13] and Ressler and Zak[14] (normal values, 80 to 120 and 230 to 350 µg/100 ml , respectively) and 24 hour urine iron excretion by the method of Fisher and Price[15] (normal values, 0 5 to 1 0 mg) ^{59}Fe half time plasma clearance was detected by the method of Lajtha[16] (normal values within the range of 70 to 120 minutes) and its incorporation into the red blood cells was tested according to the method of Beierwaltes Johnson and Solari [17] Normally 75 to 85 per cent of the injected radioactive iron is detected in the red blood cells 8 to 12 days after the injection The above mentioned tests, except for the blood volume urine iron excretion, and ferrokinetics, were performed on days 3 9 12, and 15 following admission of patients with AMI Blood volume and ferrokinetic studies were made on day 15 Patients of the control group were examined on day 1 after their admission

Results

ECG *In 10 of the patients there were findings compatible with anterior wall MI, in four, posterior inferior, in two posterior wall MI* Eight patients showed premature auricular or ventricular beats or conductive disturbances Bradycardia of 35 beats per minute due to complete A V block was noted in one patient The ECG was normal in all but one patient of the control group, this patient had attacks of supraventricular tachycardia

Blood examinations The results of routine blood examinations and the blood volume values in AMI patients and control subjects are given in Table I Except for an initial leukocytosis in most

Table IV Serum iron total iron binding capacity and iron excretion in urine in patients with AMI and control subjects

	AMI patients					*Control subjects day 1*
	Day 1	*Day 3*	*Day 9*	*Day 12*	*Day 15*	
Iron (μg/100 ml)	34 3 ± 19	28 6 ± 15 7	64 9 ± 8 2	90 ± 20 5	98 3 ± 26.8	105 4 ± 22.5
TIBC (μg/100 ml)	335 ± 4 2	361 ± 45 8	361 + 34 8	399 ± 55 6	386 ± 35.9	408 ± 69 6
Iron in urine (mg/24 hr)	0 75 ± 0.3				0 71 ± 0 11	0 48 ± 0 13

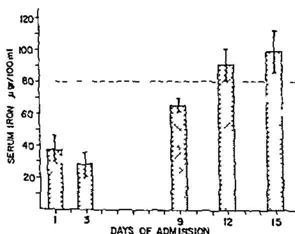


Fig 1 Serum iron levels of patients with AMI at different days after admission The dotted line marks the lower limit of serum iron in controls

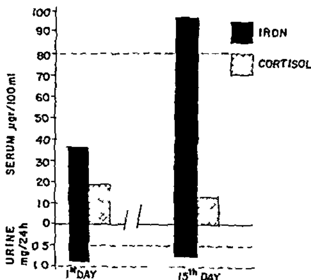


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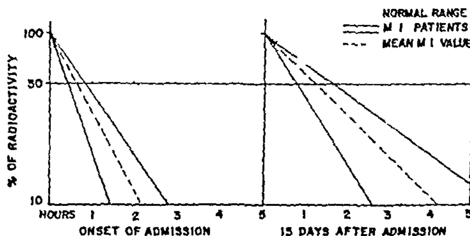


Fig 3 Half time [59]Fe plasma clearance in patients with AMI at the onset and 15 days after admission

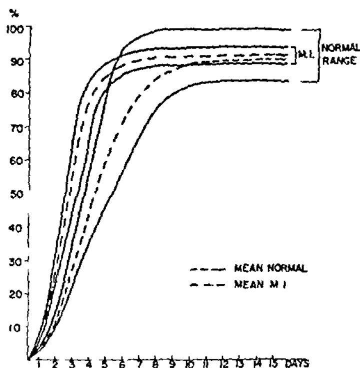


Fig 4 [59]Fe utilization curve in patients with AMI as compared with normal control subjects The range and mean values are shown

utilization curve of patients with AMI is shown in Fig 4 Ninety per cent of the radioiron was incorporated in the red blood cells by day 6

The plasma iron transport rate* is normally in the range of 20 to 40 mg per day In patients with AMI, this value on day 1 ranged from 20 0 to 70 24 mg per day (mean, 36 92) The iron metabolism could be regarded as generally almost normal in these patients the high value of 70 24 mg per day is the exceptional one and it was found in the patient with polycythemia

*Calculated from the formula

$$\frac{\text{plasma iron } (\mu g/100\ ml)}{\text{half time clearance (min)}} \times \text{plasma volume (ml/Kg)}$$

Discussion

The results of the present study confirm previous observations of a decrease in serum iron in patients with AMI [1,2] We were able to show that this decrease in the acute phase of the disease is due to rapid iron plasma clearance The normal iron plasma transport rate does not support the possibility of impaired iron metabolism, the rapid iron plasma clearance and the early incorporation of iron into the red blood cells show that the plasma iron in patients with AMI is mostly cleared by the cells of the bone marrow It cannot be excluded that some of the iron is incorporated into the reticuloendothelial cells of other organs such as the liver and spleen The patients' condition did not permit a more detailed tracing of the radioiron

We can find no explanation for the decrease in serum iron in patients with AMI Myhrman and Wilander[2] suggested that it is a result of the inflammation which usually accompanies infarctions It has been shown that producing a sterile abscess in animals by injection of therebentine decreases serum iron by 50 per cent [15]

The decrease of serum iron in our patients with AMI cannot be explained by the mechanism of inflammation principally because of the increased iron incorporation into the red blood cells which is not the case in patients with inflammation Lajtha[16] reported low serum iron with rapid iron clearance and low incorporation into the red blood cells in cases of inflammation Kampschmidt and Upchurch[17] proposed a humoral mechanism activated by endotoxins

Although the urinary excretion of iron in AMI patients was slightly higher than in control subjects the amount of iron excreted was still in

the normal range and could not explain the lower serum iron in these patients To the best of our knowledge heparin administration has no effect on ferrokinetics As for the coumadin its effect on the ferrokinetics may be excluded since the different results of these studies at the onset and 15 days after admission were obtained when the patients were on continuous anticoagulant treatment Steroids have been shown to have a siderопenic effect Prinzie and Lederer demonstrated a 64 per cent decrease in serum iron 16 days after cortisone administration to rats A similar effect was found by Lederer[21] in patients treated with 10 mg of prednisone per day for 3 to 5 months Increase of plasma cortisol has been demonstrated in patients with AMI Logan and Murdoch[22] reported a threefold increase of plasma cortisol in the majority of their 46 patients with AMI during the first 10 hours following the event The values had fallen to normal 90 hours later

Patients with AMI in the present series showed an increase in 11 OHCS which occurred mainly in the evening hours Although this increase was not as pronounced as the cases quoted in other reports[2] it is possible that it caused a decrease in the serum iron Patients in the present study receiving steroids or with diseases acting as stress factors did not show sideropenia but these conditions differ in many aspects from the stress accompanying AMI

Summary

Serum iron levels were determined in 16 patients with AMI at different days following the event and in five patients either treated with steroids or suffering from diseases acting as stress factors Patients with AMI showed a marked decrease in serum iron concentrations the lowest value being recorded at day 3 after the event serum iron returned to normal level at day 12 These alterations in iron concentration were not accompanied by changes in the 24 hour urine excretion of iron On the other hand a significant shortening of the half time ^{59}Fe plasma clearance and an early increase in ^{59}Fe incorporation into the red blood cells were found immediately after the event These values returned to normal in all but one patient who had in addition polycythemia

In the five patients comprising the control group serum iron iron excretion in urine and ferrokinetics were within the normal limits at all times

Since in AMI patients the 11 OHCS values were found to be significantly higher on the day following the infarction than on day 15 after the event, it is suggested that the decrease in iron concentration in these patients may be connected with changes in plasma 11 OHCS levels

We are indebted to Dr Lubin from the Radioisotope Institute for his helpful advice to the heads of medical departments of Beilinson Hospital Petah Tiqva for the opportunity to study some of their patients and to Drs J Ben Bassat and A. Hershko for their helpful suggestions

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Patterns of atrioventricular conduction in children

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Introduction of His bundle electrography in clin ical cardiology has helped to clarify the mecha nisms of arrhythmias and conduction defects in the human heart This technique has been used to determine the atrioventricular (AV) conduction times [1] the response to atrial pacing [2] and to study conduction patterns by extrastimulus technique [3] Data on refractory periods are lacking in chil dren however since the submittal of this manu script a paper on this subject has been pub lished [34] The heart rates of children are faster than those of the adult and their conduction system is relatively free from atherosclerotic and degenerative heart disease Therefore it is reason able to expect that the conduction system data will be different from those of the adults We have studied the response of the A V conduction system to atrial pacing and atrial premature depolarization (APD) in children with normal conduction

Material and methods

Studies were performed on 20 children with no evidence of conduction disturbance on routine scalar electrocardiogram (ECG) being catheter ized for congenital or acquired heart disease Their ages ranged from eight months to 18 years Their clinical and ECG diagnosis are listed in Table I All recordings were performed in the postabsorbtive state under Demerol 1 mg per pound Phenergan 0 5 mg per pound and Spar ine 0 5 mg per pound sedation None were on cardioactive drugs at the time of study

Recording technique His Bundle electrograms (HBE) were recorded by placing an appropriate size tripolar catheter close to the tricuspid valve [1] A quadripolar catheter was placed in the right atrium and its distal two poles were utilized for recording high right atrial electrogram and the proximal two poles for atrial pacing Simulta neous ECG Leads I II and III were recorded Both catheters were introduced via femoral veins by percutaneous introduction technique All recordings were made on Electronics for Medicine DR16 multichannel recorder at paper speeds of 100 and 200 mm per second Stimuli were deliv ered to the right atrium by a Grass stimulator Model DS88

Atrial pacing was performed to the maximum of 300 beats per minute and/or until Wenckebach block developed Refractory periods were meas ured by the extrastimulus technique [3] The right atrium was driven at the slowest possible rate that insured reliable atrial capture by the basic driving stimulus (S_1) A test stimulus (S_2) was introduced after every tenth beat S_2 was deliv ered in late diastole and moved progressively earlier by 10 to 20 msec decrements in successive test cycles

The AH and HV intervals were measured as previously described [1] A H and V represent the atrial His Bundle (H) and ventricular electro grams of the basically driven beats A_2 H_2 and V_2 represent the atrial H and ventricular electro grams in response to S_2

Definitions The A V nodal effective refractory period (ERP) is the longest A A_2 interval which does not propagate to H A V nodal functional refractory period (FRP) is the shortest interval between two successive H responses both propa

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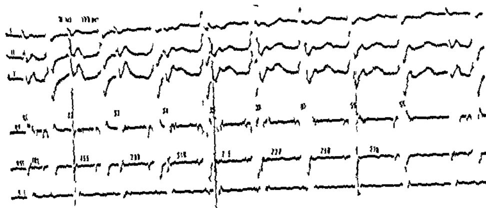


Fig 1 Demonstrates a classical Wenckebach block proximal to H which developed at the pacing rate of 180 per minute Numbers in the HBE represent the AH intervals in milliseconds

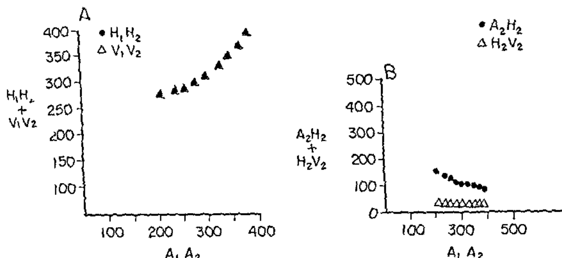


Fig 2 Delay in the A V node only A A A is plotted against H H and V V (in milliseconds) *Decreasing* A A results in shortening *of both H H and* V V *Basic* cycle length 410 msec (145 per minute) ERP A V *node 190* FRP A V node 278 *B* A A is plotted *against A H and H V* (in milliseconds) With shortening of A A the A H increases while the H V remains constant

(BB) is considered the longest H_1H_2 interval producing the appropriate ECG *pattern* of complete right or left bundle branch block (BBB)

Results of response to atrial pacing Atrial pacing was performed in 18 cases All of them developed prolonged AH as the pacing rate was increased (Fig 1) Eleven developed block proximal to H at the mean atrial pacing rate of 224 per minute ± 45 (mean ± 1 S D) Seven patients conducted 1 1 up to heart rates ranging from 150 to 240 per minute

Refractory periods To localize the site of conduction delay A_1A_2 intervals were plotted against the corresponding V_1V_2 and H H_2 intervals for each patient The following types of responses were noted

Delay in the A V node only This response was seen in four cases. Fig 2 is a representative graph from one of the patients It can be seen that as A A_2 interval shortened the H_1H_2 and V_1V_2 intervals decreased correspondingly This occurred up to an A_1A_2 interval of 210 msec At this coupling interval the H_1H and V_1V_2 intervals were 278 msec In the following test cycle when A_1A_2 interval was 200 msec A_2 was not conducted to the ventricles and was blocked proximal to H (Fig 3 C) This is the ERP of the A V node The

Table I Clinical, electrocardiographic and electrophysiologic data in 20 cases

Case No	Sex and age	Diagnosis	ECG Dx	HR	Intervals (msec.)			Response to atrial pacing		Refractory periods							
											Atrium		A V node		BB	HPS
					PA	AH	HV	Type	Rate	Pacing Rate	FRP	ERP	FRP	ERP	RP	RRP
1	M 8 mos.	PDA	LVH	150	8	112	17	Wenck	280	160	130	120	–	–	–	–
2	F 11 mos.	VSD+ DRV	IRBBB CVH	145	28	70	25	Wenck	280	170	140	130	–	–	–	–
3	M 11 mos.	NH	N	122	18	105	26	1 1	260	140	150	140	285	160	–	–
4	M 18 mos.	VSD	IRBBB	130	10	9[illegible]	30	Wenck	240	145	160	150	278	200	–	–
5	M 19 mos.	VSD	IRBBB	140	15	72	30	Wenck	280	165	180	170	–	–	–	–
6	M 24 mos.	Coarc PA	N	100 130	20	71	34	Wenck	200	140	210	200	–	–	–	–
7	F 26 mos	ASD PO PDA	IRBBB LAD	110	15	100	30	Wenck	180	115	210	200	–	–	–	–
8	F 3 yrs	PDA	LVH	145	15	95	29	1 1	240	175	140	130	–	–	–	–
9	M 4 yrs	DORV	RVH	140	10	111	30	–	–	150	200	180	–	–	–	–
10	F 6 yrs	PDA	N	117	18	85	32	Wenck	240	130	170	150	–	–	–	–
11	F 7 yrs	PO PDA	LVH	115	15	120	24	1 1	240	125	<170	<170	240	<170	–	–
12	M 9 yrs	ASD	IRBBB RAE	10[illegible]	15	82	41	Wenck	150	114	230	220	–	–	–	–
13	M 10 yrs	NH	N	91	12	100	33	Wenck	220	100	200	190	–	–	–	–
14	F 13 yrs	TA	LVH LAD	94	32	98	25	Wenck	210	110	200	190	–	–	–	–
15	M 13 yrs	A+ MR	LVH	86	10	135	44	1 1	150	10[illegible]	<220	<220	385	<220	–	–
16	M 13 yrs	PO VSD	IRBBB	86	15	80	50	1 1	180	100	<320	<320	–	–	–	–
17	M 14 yrs	AS+R	LVH Bord	90	15	86	48	1 1	180	100	240	230	240	310	–	–
18	M 15 yrs	AR	LVH	85	15	105	37	–	–	95	240	230	415	260	–	–
19	M 15 yrs	TA	LVH LAD	96	17	100	60	1 1	215	130	<180	<180	–	–	–	–
20	F 18 yrs	VSD	LAE	78	10	102	40	Wenck	180	90	230	220	350	270	435*	435

PDA Patent ductus arteriosus.
VSD Ventricular septal defect
DRV Divided right ventricle
NH Normal heart
Coarc PA Coarctation of pulmonary artery branches.
ASD Atrial septal defect
PO Postoperative
DORV Double-outlet right ventricle
TA Tricuspid atresia.
A Aortic
M Mitral
R Regurgitation
S Stenosis.
LVH Left ventricular hypertrophy
IRBBB Incomplete right bundle branch block
CVH Combined ventricular hypertrophy
N Normal.
LAD Left axis deviation
RVH Right ventricular hypertrophy
RAE Right atrial enlargement.
Bord Borderline
LAE Left atrial enlargement
Wenck. Wenckebach
* Right bundle

gated from the atrium The ERP of the atrium is the longest S_1S_2 interval in which S_2 fails to capture the atrium Atrial FRP is the shortest propagated A_1A_2 interval The ERP of the His-Purkinje system (HPS) or ventricular specialized conduction system (VSCS) is the longest H_1H_2 interval in which H_2 fails to conduct to the ventricles The relative refractory period (RRP) of VSCS is the longest H_1H_2 interval at which the H_2V_2 starts to become longer than H_1V_1 Such a prolongation suggests delay in the His Bundle distal to the recording site or bundle branches or both

The refractory period (RP) of a bundle branch

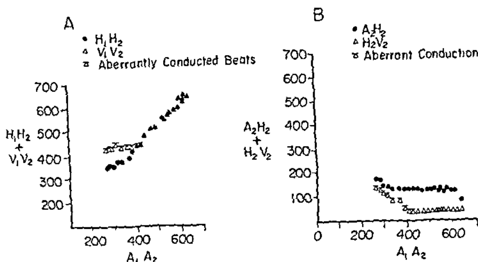


Fig 4 Delay in the A V node and HPS *A* A A is plotted against H H and V_1V (in milliseconds) See text for description *B* A A is plotted against A H and H V (in milliseconds) See text for description

produced increase in H_2V_2 which therefore represents the RRP of HPS

Block in the atrium In 11 cases the atrium proved to be the limiting factor and determined the conduction of impulses to the A V node and ventricles In these 11 cases the RP s of AV node and HPS were shorter than those of the atrium In four cases the RP s of atrium A V node and HPS were less than the shortest test cycle of 170 180 220 and 320 msec

The mean values standard deviations (S D) and standard error of the means (S E M) of the RP s are given in Table II

Table II Statistical analysis of refractory periods

Site	*N*	*Mean (msec)*	*SD*	*SEM*	*Range*
Atrium FRP	16	189	37	10	130-240
Atrium ERP	16	1/8	38	10	120-230
A V node FRP	7	313	70	27	240-415
A V node ERP	5	240	60	27	160-310

Discussion

Damato and co workers[2] reported that atrial pacing normally resulted in Wenckebach block proximal to H Dhingra Rosen and Rahimtoola statistically analyzed their experience with atrial pacing in adults and found that Wenckebach block developed at a mean atrial pacing rate of 146 per minute The mean value in our cases was much higher—224 per minute This may be due to increased sympathetic activity in children It would appear that a child who develops Wenckebach block at an atrial pacing rate less than 179 per minute (mean −1 S D) may have abnormal A V nodal function

Wit and co workers[3] utilizing the extrastimulus technique reported three types of responses in adults In Type I the delay in the A V conduction time was entirely confined to the region of the A V node In Type II the delay at longer coupling intervals was entirely in the A V node and at shorter coupling intervals in the A V node and HPS However the S_2 was blocked in the A V node before the ERP of the HPS could be reached In Type III the delay was both in the A V node and the HPS but the conduction to the ventricles failed because the APD was blocked distal to H In another study on the A V conduction system in adults Damato and co workers[5] demonstrated that the most common response to APD was for the delay to occur in both the A V node and the HPS However in our experiments the most common type of response has been the one where the atrium proved to be the limiting factor and its RPs determined the conduction of APD to the A V node and HPS The second most common response was a delay entirely in the A V node without aberration of QRS complexes In

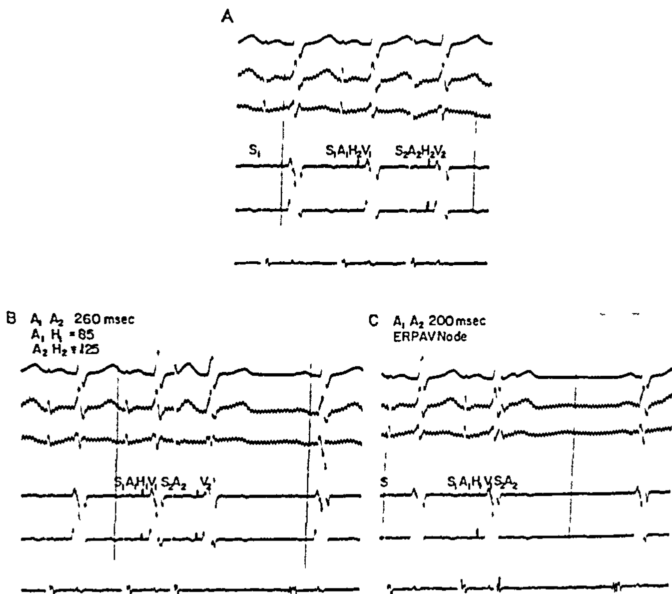
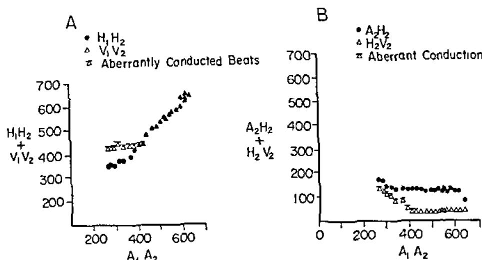


Fig 3 Delay in the A V node only *A* basic pacing performed at 145 per minute S_2 is introduced after 370 msec The A H is 85 msec A H is 95 msec and H H is 375 msec *B* decreasing the A A_2 interval to 260 msec results in A H of 85 msec and A H_2 of 125 msec H_1H is 290 msec *C* at a coupling interval of 200 msec the A is blocked proximal to H The ERP of A V node is reached at this point

shortest attainable H_1H_2 interval in this case was 278 msec which represents the FRP of the A V node

Delay in the A V node and HPS This response was observed only in one case (Figs 4 and 5) In this patient, the H_1H_2 and V_1V_2 intervals shortened equally up to a coupling interval of 410 msec (Fig 4, *A*) Decreasing the A_1A_2 interval beyond this resulted in further shortening of the H_1H_2 interval but the V_1V_2 interval remained nearly constant At a coupling interval of 270 msec the APD was blocked proximal to H (Fig 5, *D*) which indicated that the ERP of the A V node was reached The shortest H_1H_2 interval attained in this case was 350 msec which represents the FRP of A V node From an A_1A_2 interval of 430 msec onward the QRS complex showed RBBB The H_1H interval at this time was 435 msec which represents the RP of the RB To demonstrate that the delay occurred in both the A V node and HPS a curve of A_1A_2 against A H_2 and H_2V_2 was plotted (Fig 4 *B*) *It can be* seen that when A_1A_2 was shortened, A_2H_2 increased from 85 to 170 msec The H_2V_2 interval remained constant up to 410 msec coupling interval Thereafter it increased from 40 to 130 msec At A_1A_2 interval *of 430 msec the* H_1H_2 interval was 435 msec which was the longest interval that



Fg 4 Delay in the A V node and HPS *A* A A is plotted against H H and V V (in milliseconds) See text for description *B* A A is plotted against A H and H V (in milliseconds) See text for description

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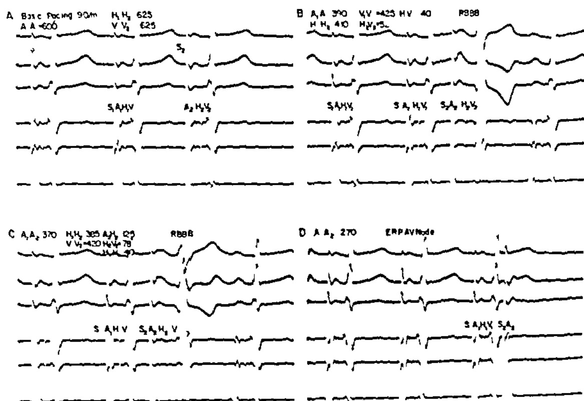


Fig 5 Delay in the A V node and HPS *A* basic pacing performed at 90 per minute At A A_2 interval of 600 msec the H H_2 and V V_2 are the same H V_2 is the same as H V (40 msec) *B* at a coupling interval of 390 msec *H_1H_2* is shorter than V V_2 The H_2V_2 is longer than H V Note the RBBB pattern due to aberrant conduction *C* further decrease in H H_2 interval at coupling interval of 370 msec H_2V_2 is markedly prolonged V V_2 has remained nearly constant *D* at A A_2 of 270 msec the A_2 is blocked proximal to H and therefore this represents the ERP of A V node

only one patient a Type II response as described by Wit and co workers[3] was noted It is conceivable that this may be due to the faster basic pacing rates which were necessary to ensure a stable atrial capture in children Denes and co workers[6] demonstrated that the A V nodal ERP increased when cycle length decreased The RP s of the HPS in their experiment decreased considerably as cycle length was shortened Therefore at faster heart rates, conduction to the ventricles was determined by the FRP of A V node as block occurs in the A V node Our patient with delay in the A V node and HPS was paced at a basic rate of 90 per minute In the other patients the basic pacing rate was 100 or more beats per minute Denes and co workers[6] could record the RP s of HPS only at cycle lengths greater than 600 msec Our only patient with a delay in A V node and HPS showed aberration of QRS complexes on extrastimulus technique Both the delay and the aberration of QRS may be related to the longer cycle length in this case At long cycle lengths the RP of the RBB is longer than the FRP of the A V node As a result the A_2 is conducted to the ventricles with H_1H_2 interval shorter than the RP of the RBB This in turn results in functional RBBB Denes and co workers[6] have shown that at the faster rates the RP of RBB and the FRP of A V node both shorten and converge and therefore at shorter cycle lengths aberrant conduction usually does not occur

In the majority of our cases we found the atrium to be the limiting factor Mendez and co workers[7] in their study on denervated canine hearts examined the effect of cycle length on the RP s They concluded that the FRP s of all cardiac tissues were decreased as the heart rate was increased In a study by Moe, Mendez and Han[8] on the canine heart epinephrine reduced the RP s of the A V node, bundle of His and bundle branches with the maximum effect on the A V node This might explain our observation that the atrium was the limiting factor since the RP s of the A V node were shorter than the RP s of the atrium

The values of the RP s of atrium A V node and HPS when compared with those obtained by Wit and co workers[3] in adults are much shorter

This again may be due to the shorter cycle length of the basic driving stimulus in our cases

Our study in children may have some limitations in determining the actual RP s because children may be apprehensive in the cardiac catheterization laboratory They may develop sinus tachycardia which may require the use of faster basic pacing rates

Summary

In this study intracardiac electrograms were performed in 20 children—ranging in age from eight months to 18 years and without evidence of conduction disturbances on the scalar electrocardiogram—to determine the normal conduction patterns response to atrial pacing and values of refractory periods Atrial pacing—18 cases—induced a prolongation of AH on increasing heart rates in all 11 developed Wenckebach block proximal to the bundle of His at the mean pacing rate of 224 per minute ± 45 (1 S D) Refractory periods were shorter than in adults Study of the pattern of A V conduction revealed three types of response (1) the atrium was the limiting structure in 11 cases (2) the delay occurred in the A V node only in four cases and (3) the delay occurred both in the A V node and His Purkinje system This response was observed in one case only

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Stokes-Adams attacks due to acute nonspecific myocarditis

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Acute nonspecific or viral myocarditis producing Stokes Adams attacks due to complete heart block is uncommon As far as we are aware, only 16 cases have been described so far[1-8] The majority of these reported cases were in male adults more than 30 years old although Loh[1] and Johnson and Lee[3] (1971) described three patients who were less than 9 years old The purpose of this paper is to describe 10 patients the majority of whom were female less than 20 years old with acute nonspecific myocarditis developing Stokes Adams attacks due to complete heart block

Material and methods

From December, 1970, to June, 1974 10 patients with acute nonspecific myocarditis and complete heart block, presenting with Stokes Adams (S A) attacks were referred to the coronary care unit, Department of Medicine, University of Singapore for cardiac pacing and intensive care management All these patients had a detailed clinical workup and were monitored continuously in the coronary care unit until their cardiac rhythm was stable or their general condition improved Laboratory investigations included the following serial blood counts erythrocyte sedimentation rate (ESR) urine analysis, blood sugar serum electrolytes blood urea tissue cultures for Coxsackie B virus in five patients, serum enzymes—creatine phosphokinase (SCPK) glutamic oxaloacetic transaminase (SGOT) lactic dehydrogenase (SLDH) antistreptolysin O titer (ASOT), hemagglutination tests for toxoplasma, anti heart antibodies antinuclear factor, serial electrocardiograms (ECG), and chest x rays T^3 and T^4 uptake studies were done in two patients All these patients have been followed up after discharge for periods ranging from 2 to 42 months

Results (Table I)

The patients ages ranged from 11 to 27 years and the majority of them (60 per cent) were less than 20 years There were more females than males (F M = 4 1) and only one patient was not of Chinese descent Fever, present in nine patients, was the earliest symptom in five patients and it was usually present for 5 days before admission to hospital Gastrointestinal (GI) symptoms were common (eight patients) and these usually preceded the syncopal episodes The GI symptoms were abdominal pain, vomiting or diarrhea and the abdominal pain was either present all over the abdomen or localized in the epigastrium Minimal hepatomegaly was seen in only two patients None of the patients had splenomegaly or significant lymphadenopathy Vague abdominal tenderness was present in six patients

Chest pain was present in only two patients and it was described as crushing and was situated in the retrosternal region All 10 patients had signs of complete heart block (CHB) at admission and four were in cardiogenic shock Two patients had clinical evidence of cardiomegaly which has persisted even at follow up An apical soft ejection systolic murmur was heard in all 10 patients and a third heart sound was heard in four Two

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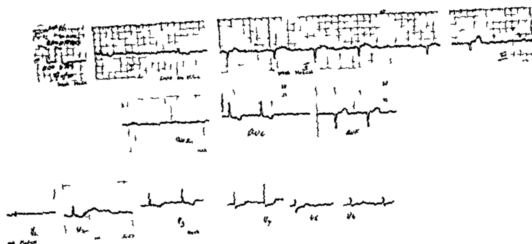


Fig 1 Case 8 ECG showing complete heart block with junctional pacemaker focus

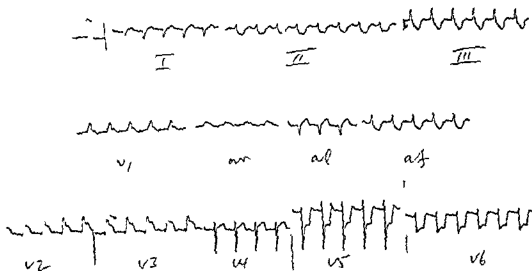


Fig 2 Case 4 ECG shows RBBB with LPH (+ 130) There is ST segment elevation in Leads V to V and ST depression in V and V₆

female patients were obviously thyrotoxic with visibly enlarged thyroid glands One patient was untreated and the other stopped treatment on her own accord several weeks before the onset of acute myocarditis A macular erythematous rash was seen in one patient (Case 2)

Laboratory investigations Four patients had leukocytosis but in only one was the total white count greater than 13 000 per cubic millimeter One patient (Case 2) had leukopenia (1 500 per cubic millimeter) and thrombocytopenia All 10 patients, except one had elevated ESR values ranging from 16 to 75 mm per hour (Westergren) Three patients had normal serum enzymes (SCPK SGOT or SLDH) and the rest had elevated values (Table I)

The ASOT values were raised in four patients their values ranging from 300 to 7 500 Todd Units and these were normal before discharge Throat swabs for bacterial culture did not reveal the presence of streptococci or diphtheria None of the patients had a positive test for toxoplasmosis anti heart antibodies or antinuclear factor The serum electrolytes were abnormal in three patients who had elevated blood urea levels

These patients had raised urea levels due most probably to cardiogenic shock their values ranging from 100 to 300 mg per 100 ml The

Table I Findings in 10 patients

Case No	Age	Sex	Symptoms: Fever	Symptoms: Pain	Symptoms: Gastro intestinal	Symptoms: S A attacks	Shock (lowest B P)	Thyrotoxicosis	ECG	Peak level of enzymes: SGOT*	Peak level of enzymes: SCPK
1	20	F	+	–	–	+	–	+	CHB (LBBB pattern) ST in II III aV_F	39 U/L	21
2	27	F	–	Chest pain	Vomiting	+	–	+	CHB (LBBB pattern)	175 KU	–
3	15	F	+	Headache	–	+		–	CHB (narrow QRS complexes) giant T wave inversion	327 KU	33
4	11	F	+	Epigastric pain	Diarrhea	+	60/40	–	CHB RBBB with LPH (+150) and first-degree heart block acute anteroseptal infarct pattern	278 KU	>[illegible]
5	26	M	+	Epigastric pain	Vomiting diarrhea	+	60/40	–	CHB (narrow QRS complexes) ST II III aV_F	46 U/L	5
6	19	F	+	Abdominal headache	Vomiting	+	50/?	–	CHB RBBB and LAH (–45) ventricular tachycardia ventricular premature beats	>400 KU	>90
7	23	F	+	Chest pain	Vomiting	+		–	CHB (RBBB pattern)	117 KU	13
8	11	F	+	–	Vomiting	+		–	CHB (first-degree heart block and RBBB pattern) transient LPH	112 KU	153
9	14	F	+	–	Vomiting	+	50/?	–	CHB with LBBB pattern nonspecific T wave inversion V_1 to V_4	370 KU	116
10	10	M	+	Abdominal pain	Abdominal distension	+		–	CHB (RBBB with LPH pattern) atrial standstill atrial flutter premature ventricular beats	128 KU	13

SGOT normal values are < 125 Kings Units (KU) or < 33 UI   SCPK normal values are < 4 5 Units.

patient with the highest blood urea was anuric for 4 days and was dialyzed peritoneally All had normal renal functions at discharge Tissue cultures for Coxsackie B virus were negative in all five patients, Patient 3 had significant titers of antibodies to arboviruses

Electrocardiogram On admission CHB with a slow ventricular rate ranging from 28 to 48 per minute, was seen in all patients (Fig 1) Two had CHB with narrow QRS complexes, indicating a high pacemaker focus The remaining eight patients showed widened QRS complexes, suggesting the presence of trifascicular disease of the conducting system ST segment depression and T wave inversion were seen in eight patients giant T wave inversion was present in Patient 3, and Patient 4 showed an acute anteroseptal infarction pattern with right bundle branch block (RBBB) and left posterior hemiblock (LPH) (+ 130°, Fig 2) Patient 4 developed ventricular tachycardia and fibrillation during CHB and she was treated with DC cardioversion and intravenous lignocaine Patient 6 had premature ventricular beats and ventricular tachycardia Nine patients had temporary transvenous cardiac pacing because of Stokes Adams attacks (Fig 3) One patient was not paced as the idioventricular rate responded satisfactorily to isoprenaline infusion

Progress Four patients had cardiogenic shock while in CHB, three remained in shock while being paced but responded to vasopressor therapy Of these three one developed ventricular tachycardia and one had ventricular tachycardia and fibrillation successfully treated with DC cardioversion

Two patients (cases 3 and 10) followed up over 12 and 8 months respectively remain in CHB but are well compensated and able to cope with their usual daily activities Except for these two patients normal A V conduction returned in the

CXR	Laboratory investigations (peak level)			
	Tw	ESR (mm/hr)	Urea (mg/100 ml)	ASOT (Todd Units)
N	11,200	64	36	604
N	11 300	75	5,	7 500
N	1,500	17	25	Neg
+	6,800	73	132	300
N	17 600	16	110	Neg
N	5 000	40	300	Neg
N	8 600	47	20	34?
+	13 000	48	27	Neg
N	8 500	5	46	Neg
+	7 900	50	26	Neg

rest In seven patients this occurred between 1 to 12 hours after the institution of cardiac pacing and in one patient (Fig 4) after 12 hours of isoprenaline therapy Temporary relapse into CHB was seen in 3 patients

At follow up six patients have normal ECG s one has an old anteroseptal infarction pattern with permanent LPH (+ 120° Fig 5) and the other has a permanent RBBB with alternating LAH and LPH

Discussion

Acute nonspecific myocarditis has been described in Singapore previously [1 4] Chao s autopsied cases were all young adults below 30 years half of whom were admitted to the surgical units for fever abdominal pain and vomiting or diarrhea simulating acute appendicitis The other half were admitted to the acute psychiatric wards for psychotic symptoms The clinical features were similar to those seen in some of our patients all of whom have survived their acute illness In this series there was predominance of young females the majority less than 20 years old Other authors[10 11] have reported the common occurrence of this condition in males and Pruitt[10] believed that males are more susceptible because of their increased physical activity during infection Two patients were frankly thyrotoxic but we believe that the development of CHB was unrelated to their thyrotoxic state and that it was due to an acute nonspecific infective myocarditis Davis and Smith[7] reported six cases of CHB in thyrotoxic patients but the A V conduction disturbance was attributed to acute infection in four and to digoxin administration in two patients Muggia Stjernholm and Houle[6] attributed the CHB to thyrotoxic myocarditis in the patient they described Our belief is supported by Goel Hanson and Han [12] who have shown experimentally that in dogs made thyrotoxic the A V conduction time and functional refractory period were shortened facilitating impulse transmission through the A V conducting system This would indicate that thyrotoxicosis per se is unlikely to produce heart block.

It is unlikely that coronary artery disease was the cause of CHB in our series because of the preponderance of young female patients although in Whitehead s[2] series one patient had severe atherosclerosis Rheumatic fever is also an unlikely cause although this cannot be excluded in Patient 2 who had an extremely high ASOT level Freidberg[13] believed and most physicians will agree that CHB is very uncommon in patients with rheumatic fever and serious conduction disturbances may not be directly due to rheumatic fever High ASOT levels have been described in patients with Coxsackie myocarditis [14] In two of our patients the high ASOT level (more than 350 Todd Units) could be due to a coexisting streptococcal infection Diphtheria is unlikely to be responsible as in our experience diphtheric myocarditis never occurs in the absence of throat manifestations

The acute presentation of fever abdominal pain chest pain diarrhea vomiting and mild leukocytosis suggests that an infective process probably an acute virus infection was the cause of myocarditis Although tissue culture for Coxsackie B virus was negative in the five patients who had it done this does not exclude a

Table 1 Findings in 10 patients

Case No	Age	Sex	Symptoms: Fever	Symptoms: Pain	Symptoms: Gastro intestinal	S A attacks	Shock (lowest B P)	Thyrotoxicosis	ECG	Peak level of enzymes: SGOT*	Peak level of enzymes: SCPK
1	20	F	+	–	–	+	–	+	CHB (LBBB pattern) ST in II III aV$_F$	39 U/L	21
2	27	F	–	Chest pain	Vomiting	+	–	+	CHB (LBBB pattern)	175 KU	–
3	15	F	+	Headache	–	+		–	CHB (narrow QRS complexes) giant T wave inversion	377 KU	35
4	11	F	+	Epigastric pain	Diarrhea	+	60/40	–	CHB RBBB with LPH (+150) and first-degree heart block acute anteroseptal infarct pattern	278 KU	>[illegible]
5	26	M	+	Epigastric pain	Vomiting diarrhea	+	60/40	–	CHB (narrow QRS complexes) ST II III aV$_F$	46 U/L	[illegible]
6	19	F	+	Abdominal headache	Vomiting	+	50/?	–	CHB RBBB and LAH (–45°) ventricular tachycardia ventricular premature beats	>400 KU	>20
7	23	F	+	Chest pain	Vomiting	+		–	CHB (RBBB pattern)	117 KU	13
8	11	F	+	–	Vomiting	+		–	CHB (first-degree heart block and RBBB pattern) transient LPH	112 KU	185
9	14	F	+	–	Vomiting	+	50/?	–	CHB with LBBB pattern nonspecific T wave inversion V to V$_s$	370 KU	116
10	10	M	+	Abdominal pain	Abdominal distension	+		–	CHB (RBBB with LPH pattern) atrial standstill atrial flutter premature ventricular beats	128 KU	13

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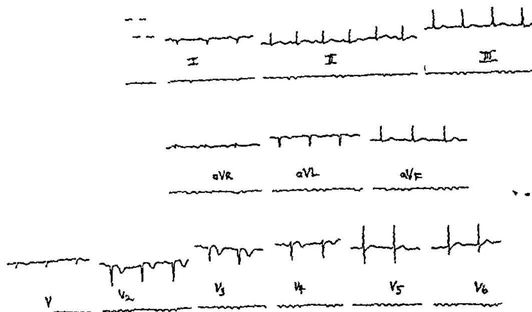


Fig 5 A 12 lead ECG of Patient 5 showing a recent anteroseptal infarction pattern with LPH (+ 120)

viral etiology as animal inoculations were not done

Cardiomegaly is considered to be one of the hallmarks of acute myocarditis [1] but it is of interest to note that this was seen in only two patients (20 per cent) and has persisted in one The degree of cardiomegaly is usually related to the extent of myocardial inflammation In those cases without cardiomegaly there could be selective involvement of strategic parts of the heart such as the conducting system Two patients with extensive myocardial damage developed shock prerenal renal failure and malignant ventricular arrhythmias. Involvement of the conducting system in these two patients is considered to be due to the extensive myocardial inflammation (cases 4 and 6) Two patients developed permanent CHB and another patient (case 6) who has bifascicular disease of the AV conducting system may develop complete heart block or asystole at a later date All three patients are being considered for implantation of permanent pacemakers The first case of transient pure LPH in acute myocarditis was described by Forfang and Lippestead In our series we have one patient (case 4) with permanent LPH and another (case 8) with transient LPH

Normal A V conduction in eight patients appeared soon after cardiac pacing was started and this may have been the result of an increased cardiac output and concomitant increased coronary artery perfusion However CHB can recur as late as 14 days after initial restoration of A V conduction and because of this pacemaker electrodes should not be removed until at least 2 weeks after restoration of normal A V conduction

The mode of death in patients with acute nonspecific or viral myocarditis may be severe cardiac failure ventricular asystole or ventricular fibrillation Death from CHB leading to ventricular arrest of asystole as a result of A V nodal disease or trifascicular disease of the conducting system is said to be uncommon [2, 3, 10] However our experience demonstrates that acute myocarditis may be a more important cause of CHB and other life threatening arrhythmias than has been hitherto suspected All these 10 patients could have died if they had not been paced and treated in an intensive care area where continuous ECG monitoring and prompt therapy can be carried out

Summary

Ten patients all below 30 years of age (8 females and 2 males) developed Stokes Adams attacks from complete heart block due to acute nonspecific myocarditis Coexisting thyrotoxicosis was present in two patients and cardiogenic shock was seen in four Temporary transvenous

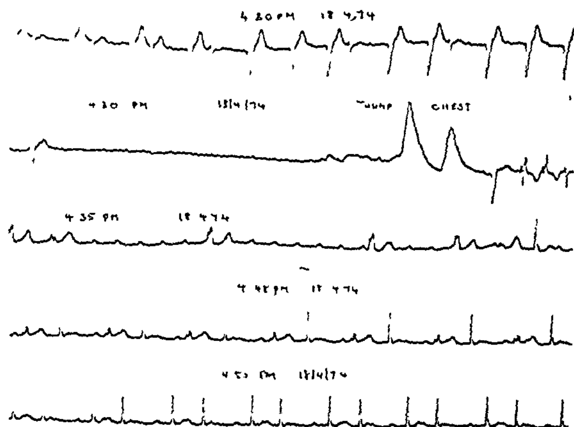


Fig 3 The second strip illustrates the effect of a thump on the chest stimulating ventricular activity after a period of ventricular arrest

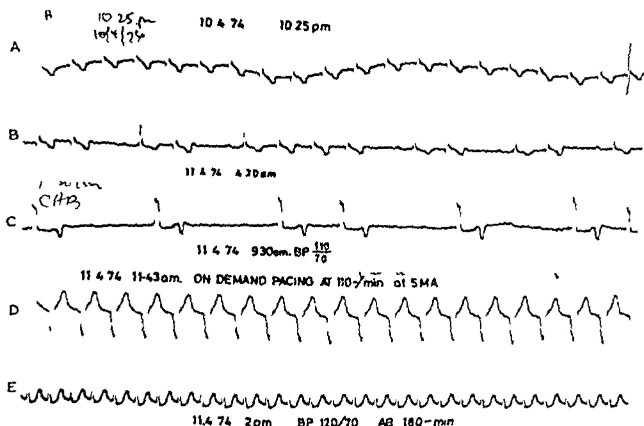


Fig 4 The last rhythm strip shows the restoration of normal A V conduction after a brief period of ventricular pacing

Early and late effects of the coronary bypass operation on cardiac contractility and coordination

Isaac Starr
Horace MacVaugh III*
Philadelphia Pa

By this study we expected both to increase our knowledge of the clinical effectiveness of this procedure and to throw light on several questions of great theoretical interest

Routine clinical studies made to assess the results of this operation have led to an interesting discrepancy many patients testify that their angina has been benefited or terminated by coronary bypass although no objective improvement can be demonstrated by the ordinary methods of cardiac examination

Information gained by cardiac catheterization is also discrepant In two studies ventriculograms taken before and after the operation showed that segmental contractility was seldom improved [2] But in a more recent study striking postoperative improvement was demonstrated by ventriculography in many cases [3]

Several reasons led us to believe that our apparatus and technique would provide better evidence on such problems Our experiments have indicated that the most important indicators of cardiac strength and coordination are related to acceleration of the ejected blood hence our interest in cardiac forces and in the derivative of the pressure pulse Evidence that the amplitudes of such records are proper measurements of cardiac strength comes not only from theoretical considerations [21] and the behavior of models [5] but also from the fact that standard methods of stimulating the heart such as exercise and adrenalin when given to healthy subjects are regularly accompanied by an increase in the size of these records [4]

Evidence that gross abnormalities of record contour are caused by cardiac asynchronism stems from experiments in which they were reproduced in models by simulating distortions of the ejection velocity curve [4, 5]

To these theoretical advantages important practical advantages are added Because our methods cause neither discomfort nor danger to the subject they can be repeated as often as we wish and contamination of our results by irregular changes in cardiac function due to fear discomfort or pain could be avoided or minimized in a way not possible to those using invasive methods In addition the long series of pulse waves and ballistocardiograms recorded at each of our tests permits blind estimates of the variability inherent in our techniques and of the consistency of cardiac performance at the time the test was made

The first of our studies of the *effectiveness* of a surgical procedure designed to improve the coronary circulation mammary artery ligation began about 20 years ago the results were negative When Dr MacVaugh became interested in the Vineberg procedure other studies followed [7] and when his interest shifted to the coronary bypass operation our collaboration continued Several preliminary reports of our work have been made [6] and one from an independent study [2] We have now studied 100 cases subjected to the bypass operation all were tested before and soon after it 47 have been retested more than one year

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pacing was instituted in all but one patient Except for two patients who developed permanent complete heart block, normal A V conduction returned in between 1 to 12 hours after ventricular pacing in seven patients and after 12 hours of isoprenaline therapy in the final patient The ECG returned to normal in six patients and all 10 patients survived their acute illness

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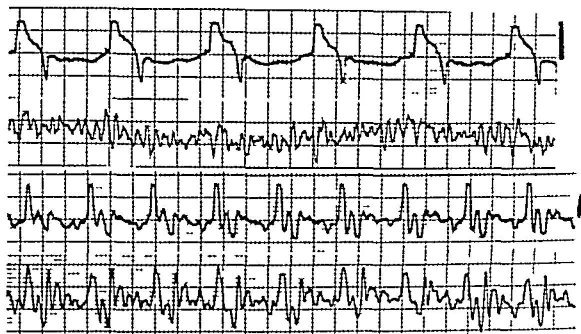


Fig 1 Carotid pulse derivative and ULF force ballistocardiograms before and after an operation bypassing three coronary arteries Patient FZ age 52 severe angina pectoris *Upper pair* taken three days before *lower pair* 12 days after operation Blood pressure at both tests 145/100 Calibration of PD bar at right = 500 mm Hg per second Calibration of BCG 15 small divisions = 275 (10) dynes for both records After operation PD amplitude doubles though this is masked by the difference in calibration PD contour changes also and maximum pressure is attained much earlier in systole After operation BCG amplitude almost doubles and the record improves in form without becoming normal

after operation, and several as long as three years after Over 400 tests have now been performed and it seems time to report on the immediate and long term effects of coronary bypass on cardiac contractility, and to compare our objective findings with the patient s subjective impressions of the clinical result obtained

Patients

The patients studied consisted of 87 men and 13 women The men averaged 51 6 years of age ($\sigma = \pm 7 8$) the women 50 7 years ($\pm$ 6 2) The range was from 35 to 67 years All were cases of coronary heart disease with coronary obstruction demonstrated by cardiac catheterization All but one were cases of severe angina pectoris the single exception being a patient who had had myocardial infarction not followed by angina

Operation

The procedure varied with the needs of each case in 29 patients an obstruction in one coronary artery was bypassed, in 41, two arteries in 19, three arteries were bypassed In most a vein was used, in some, the mammary artery

In ten cases in addition to one or more bypasses, other surgery was performed, i e valves were replaced or a left ventricular aneurysm was resected If these operative differences made any difference to the results, it is not obvious in this study to date

The Tests

The patients were tested within a week or two prior to the operation and again at the end of their hospital stay, usually about two weeks postoperatively Most of the patients returned for a third test one or two months later After this we aimed to test them at least once a year, and also if they returned for any reason between regular annual visits

To avoid the introduction of emotional factors great care was taken to reassure the patients of the innocuous nature of the tests If possible they were tested in groups those taking the test for the first time watching the test made on another before taking it themselves

The subjects lay down for 15 minutes or longer in the comfortable hammock of our ultralow frequency ballistocardiograph (*ULF BCG*) Then after calibration of the force BCG that record, the carotid pulse and its derivative were taken by techniques already described[4, 11] both during normal breathing and when the breath was held

Table 1 Pre and postoperative findings in four patients with severe angina pectoris in two patients the postoperative course did not conform to the usual pattern No important changes in blood pressure occurred

Name age	Operation	Observation and unit	Preoperative	Time of tests months postoperative 0 1	2 4	5 7	8 10	11 15	16 25	26→	Patient's estimate of result
EMcS 48	2 Bypasses	Heart rate/min	71	90	96	66		76			No angina, patient much pleased by result
		PD max mm Hg/sec	539	695	599	416		807			
		BCG amp (mm)	5 6	8 7	7 8	10 2		8 9			
		PD form	Abnormal	I	I	I		I			
		BCG form	Abnormal	S	S	I		I			
HN 44	VG to CCA LIMA to LAD	Heart rate	68	115	92			72	75		No angina patient delighted with result of operation
		PD max.	410	1 06	593			696	53		
		BCG amp	4.2	10 6	6 8			6 7	7 8		
		PD form	Normal	W	W			S	S		
		BCG form	Abnormal	W	I			I	I		
EB 55	VG to RLA LIMA to LAD	Heart rate	64	88	89	79		64	68		Patient feels tired and unwell atypical chest pains angina persists less frequently
		PD max	732	788	810	643		636	524		
		BCG amp	13 3	6 8	5 7	5.3		6 1	5 0		
		PD form	Abnormal	S	S	S		S	S		
		BCG form	Abnormal	S	S	S		S	S		
MB 45	3 Bypasses	Heart rate	74	87	91	78			56	58	Small myocardial infarction one year postoperative angina occasionally not as severe as preoperative
		PD max	711	542	652	89			528	215	
		BCG amp	8 7	10 6	8 9	7 7			5 9	7 0	
		PD form	Abnormal	I	S	I			S	W	
		BCG form	Abnormal	S	S	S			W	W	

For comparison of cardi coordination S same I impr ed W worse than before operation For changes in strength 15 mm. = 2 5 (10⁵) dynes.

in midinspiration An estimate of blood pressure by the auscultatory method completed the test

Reading the records

Fig 1 shows a small part of a typical record The 100 or more complexes in each record were first inspected for variability The selection of complexes for measurement and their number depended on this inspection the aim being to secure a sample characteristic of the whole

During normal breathing there is a respiratory variation in every force BCG and the vertical distance between the I and J wave tips of the largest and smallest complexes of three typical respiratory cycles were measured the average of the six being recorded as millimeters or dynes Whenever cardiac performance was unstable we measured and averaged far more complexes than this

PD max was calculated from the maximum slope of the conventional pulse wave front recorded at low amplification and measured to the nearest degree As a rule three typical complexes were measured and averaged but if cardiac performance was unstable many more were measured

From these two numerical indices of cardiac strength the differences found after operation were recorded usually as change from the pre operative level expressed as a per cent of that level

Changes in cardiac coordination indicated by changes in the contour of our records could not be recorded numerically The distinction between records that were normal and abnormal in contour is not always easy to make but even when made blindly a reviewer s own ratings are highly reproducible [1] In five laboratories working independently BCG abnormality has been found to be strongly associated with increased morbidity and mortality [11] But there is likely to be great variety in any large group of records judged abnormal in contour and too often we have no firm knowledge that one type of distortion indicates a more serious cardiac abnormality than another Nevertheless when one directly compares two records made on the same patient at different times it is easy to see the direction of any

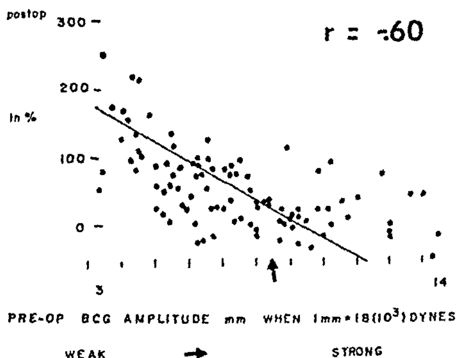


Fig 2 Relationship between cardiac strength before coronary bypass and the improvement found one to two months after *Horizontal coordinate* average BCG amplitude before operation *Vertical coordinate* postoperative change of BCG amplitude in per cent of the preoperative value i e at a level of 100 postoperative amplitude was twice the preoperative value The line is the calculated regression the arrow indicates the lower normal limit of BCG amplitude (r = –0 60) When PD max is used to indicate cardiac strength the corresponding dot diagram looks so much like the above that it has not been reproduced (r = –0 55)

change that has taken place So the contour of each postoperative record was recorded by the senior author as the same more normal, or more abnormal, than the preoperative record of that subject

Table I shows how the data secured on our patients were organized for study Data concerned with the blood pressure, not significantly changed by the operation in most cases have been omitted from Table I and play little part in this study

Results

Mortality In Dr MacVaugh s total experience with the bypass operation his operative mortality is 5 per cent, very similar to that of other surgeons The mortality of the 100 cases in this study to date is 3 per cent Obviously, no one dying in the immediate postoperative period became part of this study, but these were so few in number that the bias is negligible

The operative trauma In studies made before and after major operative procedures on organs other than the heart, the BCG has often shown temporary deterioration of cardiac function in the immediate postoperative period [4, 15] Our unwillingness to move our patients from the resources of intensive care until a week or more after coronary bypass usually prevented us from testing them immediately after operation The few tests made during the first postoperative week indicate that operative trauma may indeed cause a temporary deterioration of cardiac function which might mask the beneficial effects of the operation for several days

Subjective effects of coronary bypass The great majority of our patients reported that their angina was either improved or completely relieved our percentage of improvement is very similar to that given by other surgeons

Objective effects of the operation Given in the tables and in Figs 2 and 3 and summarized in the conclusion some explanation of our results is still necessary The early effects of the operation reaching a maximum one or two months after it, can be compared with the preoperative findings in almost all of our 100 cases (Table II) Only about ½ of these cases have been followed for a time sufficient to permit a study of later effects in these cases the results secured before soon after, and 1 5 years after operation can be compared (Tables III, IV, V and VI)

The postoperative changes in *cardiac strength* are influenced by the state of the heart before

Table II *Early effect of coronary bypass operation on cardiac contractility in 97 cases of angina pectoris studied one to two months postoperatively*

Mean changes in per cent of preoperative values		σ
Pulse rate	+35%	(± 24%)
Pulse pressure	+ 6%	(± 39%)
Systolic pressure	− 3%	(± 16%)
Diastolic pressure	− 3%	(± 17%)
PD max.	+56%	(± 79%)
BCG amp	+54%	(± 64%)

PD form improved in 43 per cent of subjects.
BCG form impro ed in 70 per cent of subjects.

operation (Fig 2) so they can best be described briefly by dividing *the data into two groups* as has been done in Table III and Fig 3

In one group a small BCG amplitude indicated that the hearts *contracted weakly* before operation and the procedure was promptly followed by a striking increase in average rate and strength which highly significant statistically restored average cardiac strength per beat to normal After this maximum improvement both rate and strength slowly declined by 1 5 years after operation the average improvement in one of our two measurements had lost its significance

In the other group the hearts contracted with *normal strength* before operation Despite an early postoperative increase in average pulse rate similar to that of the first group the average early postoperative improvement in strength per beat was so much smaller in the second group that it did not attain statistical significance in our data (Table III) The rate of decline from the maximum during the following 1 5 years (Fig 3) was similar in both groups

If one multiplies our estimates of average cardiac strength per beat by the heart rate to get an estimation of strength per minute the increase over the preoperative value at the time of maximum improvement is greatly increased (Table II) Later this gain diminishes or disappears (Fig 3)

The effects of the procedure on *cardiac coordination* are recorded in Table IV While the contour of our records was improved after operation in about ¼ of our 100 cases in only one case did both the PD and BCG contour regain normality

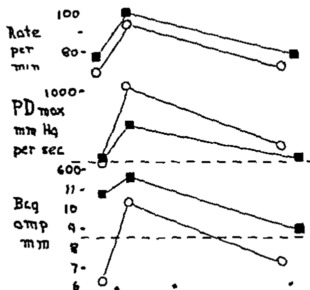


Fig 3 Average cardiac contractility before and after coronary bypass in 47 subjects *Horizontal coordinates* dots indicate six month intervals *Vertical coordinates* average heart rate and the averages of two measures of heart strength PD max and BCG amplitude in tests made before one to two months after and about 18 months after operation in 47 subjects *Solid squares* indicate averages of data secured in patients whose hearts judged by BCG amplitud were contracting normally before operation *Circles indicate averages of data* secured in patients whose hearts were judged by BCG amplitude to be contracting weakly before operation *Broken lines* indicate lower normal limits of PD max and BCG amplitude respectively *If PD max instead of BCG amplitude is used to* identify the weak hearts the corresponding figure looks so like the above that it has not been reprodu ed

So while the operation usually improves cardiac function in only one of our cases did it restore it to normal

Discussion

Inherent variability of our methods The mean difference between pairs of BCG measurement of cardiac strength taken blindly within a few minutes of one another in 16 healthy persons by the apparatus and techniques we now use is 8 per cent of the mean of each pair and $\sigma = 5$ per cent for estimates of PD max it is 9 per cent (± 6 per cent) Obviously our methods like most clinical methods are crude but such data can be easily used to establish the significance of the large changes found so often after operation in individuals such as those illustrated in Table I

Variability of cardiac function in our patients There is increasing evidence that spontaneous variation is much larger in severe cardiac disease

Table III Early and late effects of the coronary bypass operation on cardiac strength in 47 cases followed for an average of 1 5 years

	Average changes from preoperative level in per cent of this value				
	At time of maximum improvement 1 to 2 months postoperative		*t*	*At last test averaging 18 4 months postoperative*	*t*
When the heart before operation was judged to be of normal strength (i e BCG amp > 8 5 mm) n = 16	Pulse rate	+31%	4 9	+ 5%	1 0
	PD max	+26%	1 3	+ 5%	1 2
	BCG amp	+14%	1 3	−12%	−0 5
When the heart before operation was judged to be weak (i e BCG amp < 8 5 mm) n = 31	Pulse rate	+32%	7 5	+ 2%	0 9
	PD max	+72%	4 4	+20%	1 6
	BCG amp	+53%	6 5	+30%	3 9

Table IV Early and late effects of the coronary bypass operation on cardiac coordination Frequency of changes in contour from the record found before operation tested for significance

	Changes in contour at time of maximum improvement 1 to 2 months after operation (n = 44)	*Difference significant at level given below*	*Changes in contour at last test average 18 4 months after operation (n = 47)*	*Difference significant at level given below*
PD contour was *improved* in	18 (41%)		20 (43%)	
PD contour was the *same* in	19 (43%)		21 (45%)	
PD contour was *worse* in	7 (16%)		6 (13%)	
Significance of difference	7 vs 18	5%	6 vs 20	1%
BCG contour was *improved* in	29 (66%)		22 (47%)	
BCG contour was the *same* in	11 (25%)		17 (36%)	
BCG contour was *worse* in	4 (9%)		8 (17%)	
Significance of difference	4 vs 29	1%	8 vs 22	5%

Table V Changes of cardiac strength judged by combining pressure and flow data

Measurements made on each patient	Ratio
PD max 1 5 years postoperative / PD max preoperative	= 1 70
BCG amp 1 5 years postoperative / BCG amp preoperative	= 1 60
Product of ratios (related to work)	1 70 × 1 60 = 2 72
Average of products obtained in 15 subjects with strong hearts before operation	= 1 43
Average of products obtained in 21 subjects with weak hearts before operation	= 1 85
Average improvement over preoperative values found 1 5 years after operation	
In strong heart group	43%
In weak heart group	85%

than in healthy persons[7,9,10] and real danger that such variation will be confused with the effects of therapy Since our estimates of cardiac strength are expressed numerically, the ordinary statistical procedures suffice to distinguish operative effects from random variations, the values of t are given in Tables III and VI

The changes in record form which indicate changes in cardiac coordination cannot be measured numerically and the significance of these differences was tested by the 'n table for 50 per cent probability test which is based on the standard binomial expansion[16] the levels of significant difference for our data are given in Table IV Obviously, the more important postoperative differences cannot be attributed to chance variation

Controls Interesting facts emerge when our recent results are compared with those which

Table VI Comparison of subjective and objective improvement 1 5 years postoperative (subject BG omitted)

	Angina improved n = 42 mean	*Angina not improved n = 4 mean*	*Significance of differences t*
Changes in PD max in per cent of preoperative values	+11 7	−15 5	1 2
Changes in BCG amp in per cent of preoperative values	+14 2	+ 0 75	0 7
Frequencies of improvement in PD form in per cent of n	+34 0	+40 0	ns
Frequencies of improvement in BCG form in per cent of n	+47 0	+25 0	ns
Mean score of all 4 tests (see text)	1 53	0 25	2 4

followed internal mammary ligation[6] and the Vineberg operation the latter provide a control for the present study The patients were comparable all three studies were performed on cases of angina pectoris so severe that they were not doing well under conventional medical therapy From the objective tests one concludes that the mammary artery ligation accomplished nothing Assessment of the effectiveness of the Vineberg operation was handicapped by the fact that after operation all of our patients received a prolonged course of therapy with a coronary vasodilator and some received heparin as well[7] Despite the additional therapy objective improvement was small and infrequent So one can say with confidence that the marked objective improvement seen so often after coronary bypass cannot be attributed to any factor common to the operations such as anesthesia artificial respiration the opening of the chest and the surgical manipulation of the heart We have the right to believe that the greater improvement after bypass was due to increased coronary blood supply

New physiologic interpretations In the past it has been commonly assumed that the myocardium behaves as a large unit the properties of which could be inferred by observing the behavior of a small part of it the isolated muscle strip in physiologic experiments or the forces detected by a strain gauge applied between two points on the myocardium Certainly such experiments have taught us much

But to us the evidence is now overwhelming that in advanced coronary heart disease the myocardium does not perform as a unit but breaks up into many parts some of which contract more weakly than others some later than others * This incoordination was seen during ventriculography in many of our patients and when the observer s vision is limited to the margins of the ventricular silhouette in a plane at right angles to the line of vision much more abnormal action must be missed than can be seen There was other evidence of cardiac incoordination in the distorted contour of the BCG PD or both found in all but three of our 100 patients with coronary heart disease

This cardiac incoordination complicates the interpretation of our estimations of cardiac strength for the more normal parts of an incoordinate heart by contracting more strongly could mask the weakness of a weak part in our tests doubtless that is the reason why so many bad hearts judged to be incoordinate because of the distorted contour of our records give no evidence of weakness in our tests But the asynchronism of a bad part cannot be masked by improved contraction of a normal part as far as we can see indeed BCG s normal in contour are real rarities in this series of severe cases of angina The performance of the sick heart is proving to be much more complicated and much more difficult to describe simply than was previously believed

Combining BCG and PD evidence Differences in the physiologic information carried by our records must also be kept in mind The BCG is related to blood flow [2] the pulse to blood pressure Used to measure cardiac coordination the BCG is more sensitive than the more highly damped pulse simultaneous records showing a normal PD contour and a distorted BCG contour are common Used to measure cardiac strength averages obtained by the two methods usually agree well (Tables II and III) but in certain individuals the heart may be judged strong by the BCG and weak by the PD or vice versa Such apparent inconsistencies can be explained physiologically as due to differences in peripheral impedance[3] and such findings raise the question whether a better index of cardiac strength could

not be secured by multiplying PD max by BCG amp and defining cardiac strength empirically in terms of the product Work as defined by Newton ($\int$ pdv) is estimated from the products of flow and pressure measurements The product of our two measurements would be in given units which have no short name and which are altogether unfamiliar

Nevertheless it did seem of interest to compare the relative size of the postoperative changes in our two methods of judging cardiac strength and this has been done as is shown in Table V the use of ratios keeping the calculation "dimensional" The conclusions concerning the effectiveness of the bypass operation drawn from the product of the two ratios (Table V) are similar to those already stated in Tables II III and IV the early postoperative increase in cardiac strength the greater improvement in hearts judged to be weak before operation and the later loss of part of the early gain are clearly shown Indeed the results of this unorthodox calculation suggest that the average gain of cardiac strength persisting 1 5 years after the operation is larger than is estimated when either the BCG or PD is used alone (Table V)

On the decline which follows early postoperative improvement Regression equations giving the rate of decline of the BCG amp and PD max of healthy persons as age advances [11] are available for comparison with our new data We have also been following 12 cases of mild angina under medical treatment for an average of six years each [1] the average rate of decline of force BCG amplitude as age advanced was very close to the slope of the regression of healthy persons as age advanced

The average postoperative rate of BCG decline from the postoperative maximum (Fig 3) is over five times faster and the corresponding decline of PD max over 10 times faster than is found in healthy persons as age advances Extrapolation of the falling lines of Fig 3 suggests that the operative gain will be extinguished in about three years but there is good reason to think that such a view is too pessimistic Twenty one of our cases have been tested about six months postoperatively and a year or more later, the average rate of fall beginning six months after operation is much slower than the fall from the maxima shown in Fig 3 Apparently, in many cases the curve of decline is concave upward leaving some cases on a plateau of improvement which so far, shows no signs of diminishing the first and second cases in Table I are examples

Is the fall from the maximum due to closure of the bypass? Lack of information about the adequacy of collateral circulation makes the demonstration of a narrowed or occluded coronary artery difficult to interpret physiologically Before operation cardiac catheterization demonstrated that one or more coronary arteries were narrowed or blocked in all our cases although evidence of an old infarction was present in very few In many patients our tests showed that cardiac contractility was not reduced in strength despite demonstrated coronary artery abnormality, apparently the narrowed orifice or collateral circulation, or both supplied blood enough to permit normal cardiac function as long as these patients were at rest

The aim of the bypass operation is to relieve symptoms and to restore the heart as a pump We believe that our tests of contractility provide better objective evidence of the success or failure of the procedure than a demonstration of arterial patency or occlusion would do Such considerations made us unwilling to subject our patients to a second cardiac catheterization as long as they were doing well

Thirteen patients were catheterized after operation the bypass was found to be occluded in five, and patent in the remainder In ten patients this information could be compared with the rate of decline of cardiac strength after the maximum operative improvement In the seven patients whose bypasses were open the averages of the rates of fall were for PD max 415 mm Hg per second per year (σ ± 310) and for BCG amplitude 3 2 mm per year (± 3 4) In the three patients whose bypasses had closed the corresponding averages were 603 (± 466) and 2 0 (± 0 41) neither mean is significantly different from the preceding largely because of the small numbers

One important conclusion seems evident while closure of the bypass, if it occurs may well be a factor in the late postoperative deterioration in some of our cases, a patent bypass does not prevent the slow fall of cardiac strength seen so commonly in our patients after maximum postoperative improvement

Comparison of subjective and objective criteria of operative success The well known difficulties of subjective evaluation of a therapeutic procedure complicate the interpretation of the few discrepant cases in our data Thus one man (BG) showed persistent postoperative improvement in all four of our objective tests and soon after operation he reported that his angina was improved But later he said that his angina was worse a change of story which coincided with an application for compensation for total disability which was eventually granted Two years and five months after operation he still complained bitterly of angina while all his objective tests still showed improvement Perhaps the source of the pain was a lesion too small to affect cardiac performance when measured by our tests but the bias was so clear that we excluded these data from the final statistical analysis

Six subjects claimed relief of angina although we could find no objective evidence of improvement and in five of them a physiologic explanation suggests itself The hearts of these five subjects although incoordinate contracted with normal strength when tested before operation evidently despite the narrowed coronaries there was sufficient blood supply at this time So despite the fact that more blood had been made available by the bypass the excess supplied no need and had no demonstrable effect as long as the subjects were at rest during exertion the extra blood must have served a useful purpose for angina was either relieved or improved

In all the 40 other cases followed for over a year the objective and subjective findings agree quite well (Table VI) though the attainment of statistical significance was rendered difficult by the fact that the number of those denying subjective benefit was so small

The average improvement in PD max and BCG amp was much larger and improvement in BCG form almost twice as frequent in those whose angina was better after operation but none of these differences attained significance by themselves Therefore a score for total objective improvement was secured by assigning each patient one unit whenever PD max improved over 20 per cent after operation another unit if BCG amp improved similarly and others if PD or BCG or both improved in form Thus cases showing no objective postoperative improvement of any kind were rated 0 those in which all tests improved 4 Table VI shows that the mean objective improvement score is much larger in those subjectively relieved and this difference significant at the 5 per cent level narrowly misses the 1 per cent level

The findings after coronary bypass and the older concepts of ischemic heart disease Cardiac catheterization showed that obstruction of one or more coronaries was present in all the patients admitted to this study when myocardial weakness accompanied it one can set up the hypothesis that this weakness was due to reduced blood supply The operation supplies an experimental test of this hypothesis When surgical restoration of the coronary circulation caused the weakness to disappear as was true in many of our subjects the hypothesis is strongly supported Indeed we believe that this is the best evidence of an ischemic factor in heart disease that has been brought forward But in a minority of our subjects with weak hearts no improvement in cardiac strength followed the operation while this may have been due to technical imperfections in its performance, we suspect that intrinsic myocardial weakness may well play an important part in many of these very sick patients

The fact that improvement in angina follows coronary bypass in such a high percentage of patients affords far stronger support to the classic theory relating this symptom to cardiac ischemia than does the indirect evidence available before

Our findings and the older clinical tests This presentation would be incomplete without a discussion of a most important question why is it that the cardiology of the recent past based on physical findings blood pressure palpation of the pulse the x ray and the ECG fails to detect the marked cardiac improvement which so often follows the coronary bypass operation? In the past clinical interest has centered on anatomic diagnosis and the methods used routinely by doctors do not provide the physiologic information needed to judge the success or failure of therapeutic procedures such as the bypass operation designed to improve the strength and coordination of the cardiac pump

Summary

In 100 cases of coronary heart disease, cardiac contractility was studied before and after coro

nary bypass by a flow method, the force ballisto cardiogram, and by a pressure method, the carotid pulse derivative The two methods gave very similar results in most cases, and the agreement of their averages was impressive A marked increase in cardiac strength, reaching its maximum a month or two after operation followed the procedure in most cases Cardiac coordination was also improved at this time in many subjects, but complete cardiac normality was very rarely attained

This early postoperative improvement was greater in hearts judged to be weak before operation than in those judged to be normal in strength

The early cardiac improvement was seldom held in its entirety, but usually declined at a rate which if continued, would abolish the postoperative improvement in about three years This rate of cardiac decline was many times faster than that found in healthy persons or in unoperated cases of mild angina as age advanced Nevertheless in over 1/3 of our cases followed for a year and a half or longer, their hearts were still stronger or better coordinated or both than they had been before operation and there is reason to believe that the decline was leveling

At their last test, the great majority of patients still reported that subjective improvement in their angina continued This subjective improvement was significantly related to objective improvement of cardiac contractility in our data, but there was one striking exception to this rule

Previous studies of results following internal mammary artery ligation and the Vineberg procedure afford an important control to the present work

The cardiac catheterizations performed at the University Hospital were done under the direction of Dr James C Shelburne who also assisted us in the interpretation of such results Dr Samuel Askowitz assisted us by applying certain significance tests based on the binomial expansion to our data

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Nonbacterial thrombotic endocarditis in a Japanese autopsy sample A review of eighty cases

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There have been many published reports on the subject of nonbacterial thrombotic endocarditis (NBTE) since this pathologic entity was described by Ziegler in 1888[1-8] Interest in the process has continued in part because there remain unanswered questions surrounding the reported etiologic relationship to wasting disease primarily cancer and also because of the increasing realization that these valvular verrucae or thrombi may not be merely an unimportant accompaniment to a terminal illness but actually the cause of significant clinical signs and symptoms

There are several reasons for providing this additional retrospective pathologic study on the subject First, the Atomic Bomb Casualty Commission (ABCC) autopsy program provides computerized information relating to a fixed sample of atomic bomb survivors and controls with autopsies sought irrespective of cause of death or whether death occurred in the home or hospital. Although the ABCC sample is not completely representative of the general population in that it is weighted toward radiation exposed survivors, it should be possible nevertheless, to discern the prevalence of NBTE in this autopsy population and to establish whether it has occurred with excessive frequency in association with certain underlying disease processes Second this type of analysis of NBTE among Japanese has not been reported before and although there is no reason to suspect a racial difference in the pathogenesis of NBTE an opportunity is presented to study the disease process in a setting of cardiovascular disease quite different from that of Western countries[9]

Materials and methods

All Hiroshima ABCC Life Span Study[10] autopsies in which the postmortem diagnosis of NBTE was recorded in the period 1953 1970 have been reviewed, with re examination of the histologic sections and gross descriptions in all cases Adequate histologic sections of verrucae and underlying valve tissue were available for study in 59 autopsies Special stains including trichrome elastic and gram stain were used as indicated Prior medical records were also reviewed when available but these constituted such a small group that no statistical use was made of these clinical data Cases were entered into the study as NBTE if they satisfied the generally accepted criteria for this process namely single or multiple easily detached and friable vegetations consisting

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Table I Prevalence of nonbacterial thrombotic endocarditis at autopsy by sex

Sex	Total			Associated with malignant neoplasm			Not associated with malignant neoplasm		
	Autopsies	NBTE	Prevalence (%)	Autopsies	NBTE	Prevalence (%)	Autopsies	NBTE	Prevalence (%)
Male	1 739	29	1 7	604	20	3 3	1 135	9	0 8
Female	1,665	51	3 1	540	30	5 6	1,125	21	1 9
Total	3 404	80	2.4	1 144	50	4 4	2,260	30	1.3

Eighth ICD 140-209

Table II Prevalence of nonbacterial thrombotic endocarditis at autopsy by age at time of death

Age	Total			Associated with malignant neoplasm			Not associated with malignant neoplasm		
	Autopsies	NBTE	Prevalence (%)	Autopsies	NBTE	Prevalence (%)	Autopsies	NBTE	Prevalence (%)
< 60	715	6	0 8	270	4	1 5	445	2	0 4
60-69	915	21	2 3	383	16	4 2	532	5	0 9
70-79	1 099	38	3 5	356	21	5 9	743	17	2 3
80+	675	15	2 2	135	9	6 7	540	6	1 1
Total	3 404	80	2 4	1 144	50	4 4	2,260	30	1 3

primarily of platelets and fibrin attached to cardiac valves which themselves did not reveal evidence of destructive or acute inflammatory change There was no evidence of bacterial invasion of the vegetations or valve leaflet in any accepted case

Results

Prevalence sex age and associated primary diseases Tables I and II indicate the prevalence of NBTE by sex and by age groups with further breakdown according to the presence or absence of associated malignant neoplasia Of 3 404 autopsies performed during the 1963 1970 period there were 80 cases in which NBTE was among the listed postmortem diagnoses and which satisfied the above criteria Table I reveals that there was a preponderance of females among the NBTE group although the total autopsy series was almost evenly divided between the sexes and this preponderance was evident in patients with and without malignancy as an underlying disease Although 21 per cent of the autopsy group were below 60 years of age at the time of death (Table II) NBTE was clearly associated with the older age group (over 60 years of age) in both the malignancy and nonmalignancy cases

With regard to the question of whether NBTE has a predilection for certain underlying disease processes it is evident from the tables that NBTE was more prevalent in the group with malignant neoplasia than among those without malignancy Fifty of the 80 cases of NBTE were found in the malignancy group which amounted to only one third of the autopsy population A highly significant ($p < 0\ 001$) relationship with neoplasia was noted in both sexes and in both the age groups above and below 60 years of age

An analysis of the prevalence of NBTE among malignancies arising in different primary sites is presented in Table III and this table reveals that this entity was seen with significantly greater frequency in cancer of the large intestine rectum and female genital organs (no NBTE cases were associated with malignancy of the female bladder code 188) The most common malignancy in the total series was cancer of the stomach in which the NBTE prevalence was 4 0 per cent A rather high prevalence was calculated in cases of malignancy of the buccal cavity pharynx and thyroid

Table III Prevalence of nonbacterial thrombotic endocarditis by underlying principal disease at autopsy

Eighth ICD	Underlying principal disease at autopsy	Autopsies	NBTE			
			Observed	Expected	Prevalence (%)	O/E
Malignant neoplasm						
140-149	Buccal cavity and pharynx	10	1	0 4	10 0	2.5
150	Esophagus	38	3	1 6	7.9	1.9
151	Stomach	373	15	16 1	4 0	0.9
153 154	Large intestine and rectum	64	7	3.1	10 9	2.3
155-157	Liver gallbladder bile ducts and pancreas	154	5	7.3	3.2	0.7
161 162	Larynx trachea bronchus and lung	178	6	7 9	3 4	0 8
180 183 188	Female genital organ and bladder	96	10	5.2	10 4	1.9
188	Male bladder	12	1	0 5	8.3	2 0
193	Thyroid gland	6	1	0.3	16 7	3 3
	Other malignant neoplasms	213	1	7 6	0 5	0 1
Non neoplastic disease						
011	Pulmonary tuberculosis	159	2	1 6	1.2	1.3
400-414	Heart disease	314	4	4 5	1 3	0 9
430-438	Cerebrovascular disease	645	5	9 3	0 8	0 5
480-486	Pneumonia	99	3	1 3	3 0	2 3
490-493	Bronchitis emphysema and asthma	61	2	0 9	3.3	2.2
530-537	Diseases of esophagus stomach and duodenum	49	2	0 7	4 1	[illegible]9
590	Pyelonephritis	43	1	0 7	2.3	1 4
	Other diseases	890	11	11 0	1.2	1 0
Total		3 404	80	80 0	2 4	–

and in Hodgkin's disease but these groups were small in number

Of interest was the rather large number of cases of NBTE among patients dying with the principal autopsy diagnosis of pneumonia and the possibility was considered that perhaps acute pneumonia was the underlying etiologic factor responsible for the appearance of NBTE even in the malignancy group However when this question was analyzed further it was found that there were 21 NBTE cases among 423 individuals who died with autopsy evidence of both malignancy and acute pneumonia (4 9 per cent) and 29 NBTE cases among 694 autopsies (4 2 per cent) in which malignancy was not associated with pneumonia This would not seem to indicate that acute pneumonia was a predisposing factor in the appearance of NBTE

No correlation was found between the prevalence of NBTE and dose of ionizing radiation among atomic bomb survivors when the group was examined as a whole or when separated into malignancy and nonmalignancy subcategories

Pathologic findings Nonbacterial thrombotic lesions were located upon the aortic valve in 38 cases upon the mitral valve alone in 33 cases and verrucae were demonstrated on both valves in nine other cases It is of interest that in this series no lesions were apparent in relation to tricuspid or pulmonary valves The verrucal lesions were often multiple and they were always located upon that surface of the leaflets exposed to the flow of blood passing through the open valve namely the atrial surface of the mitral and ventricular surface of the aortic leaflets Measurements were available for 52 verrucae They varied from 1 to 20 mm in longest diameter (average 5 8 mm)

The vegetations consisted of amorphous acellular masses of light staining (hematoxylin and eosin) material which with the special stains resembled a mixture of fibrin and platelets No growth of endothelium to cover the surface of the verruca could be demonstrated No bacterial or inflammatory cellular reaction or infiltration were seen in either the vegetations or the underlying valves Grossly valvular thickening was present in 42 of the 59 cases examined In 23

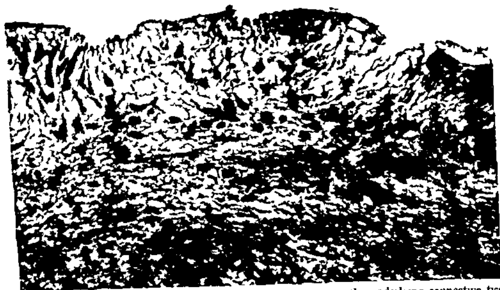


Fig 1 The endothelial lining is interrupted in three places exposing the underlying connective tissue The subendothelial tissue contains proliferating fibroblasts



Fig 2 A focus of fibrin deposition on the valve

instances it was described as nodular in 15 cases as irregular thickening and in four cases as granular There was no correlation between this gross description and any particular type of microscopic findings However two types of microscopic change were found in the valves which appeared to represent stages in the progression and development of the valvular lesion In the early stage there was degeneration and loss of endothelial cells and dissociation of collagen fibers in the subendothelial tissue (Figs 1 and 2) The endothelial cells varied in size and shape These changes were seen in 14 cases In the later stage there was loss of endothelial cells prolifera

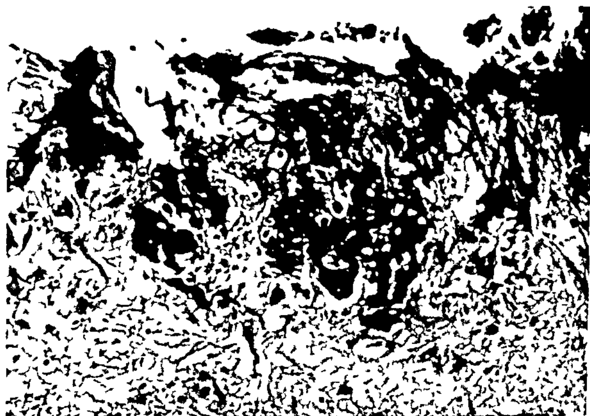


Fig 3 An advanced lesion with connective tissue proliferation into the thrombus.

tion of subendothelial connective tissue and infiltration of fibroblasts into the vegetation (Fig 3) This change was seen in 22 cases Both types of change were seen in 15 instances and in eight cases no valvular lesion of any type was recognized In no instance were microscopic stigmata of rheumatic disease or other specific endocarditis found

Severe coronary atherosclerosis or occlusive atherosclerotic coronary disease was not encountered in any case, though slight to moderate atherosclerosis was a frequent finding

A statistical analysis of thromboembolic sequelae of NBTE was not thought possible in this retrospective study due to the difficulty in differentiating embolic lesions from other vascular disease by routine methods of examination and because clinical information concerning the terminal course was not available in most cases However, it is of importance that in at least 17 cases in this series there was evidence of thromboembolic ischemic lesions, three of these with cerebral infarctions only the remainder with demonstrated single or multiple infarctions in the brain myocardium kidney spleen and thyroid gland There were six cases with myocardial infarction all showing at the most minimal coronary atherosclerosis It may also be of interest that in four cases the typical miliary lesions of myocytolysis were present as described by Schlesinger and Reiner,[11] one without associated myocardial infarction In two cases the small intramural arteries contained multiple thromboemboli These four cases were identified during a separate search for myocytolysis among the ABCC autopsy series and only 13 of the 80 NBTE cases had been scrutinized carefully for this myocardial lesion It is, therefore, possible that myocytolysis a pathologic entity quite suggestive of microscopic infarction was underestimated in this study

Discussion

There have been thorough reviews of the English literature concerning nonbacterial thrombotic endocarditis published in recent years [8] and we are aware of four case reports and a small series of NBTE in the Japanese literature [12,13] Much of the data contained in the present report are in general agreement with the earlier reported findings outside of Japan The incidence of NBTE among the entire autopsy series (2 4 per cent) is somewhat higher than reported by others, but this may perhaps be explained by the large number of older individuals in the present series The greater incidence among females can be partially explained by the fact that, in this series at least there appears to

be a relationship between NBTE and cancer of the female genital tract

Relationship to underlying disease processes NBTE has been considered by most authors to be an accompaniment of chronic wasting fatal illness most frequently neoplastic This concept has obvious etiologic diagnostic and therapeutic implications and it therefore justifies closer analysis

The distribution of accompanying disease processes in the present study usually identified as the underlying cause of death is listed in Table III Although most authors have in the past noted the frequency with which certain neoplasms have occurred in their study groups of NBTE only Rosen and Armstrong[7] have given data on the incidence of NBTE among different forms of cancer Whereas pancreas and stomach cancer had appeared in greater numbers in earlier studies of NBTE[6, 2] Rosen and Armstrong[7] supplied the statistically more significant information that NBTE appeared with increased frequency among their patients with bronchiolar carcinoma (7 7 per cent) and adenocarcinoma (7 1 per cent) of the lung and adenocarcinoma of the pancreas (3 7 per cent) It is then surprising to note the contrast with the present series in which there was a much stronger association with neoplasms of the lower gastrointestinal tract and female genitourinary system whereas only six cases of NBTE were recorded among 178 patients with neoplasms of the respiratory tract and lung We have at the present time no reason to suspect that these contrasting figures relating NBTE and tumors of certain primary sites at the Memorial Hospital in New York City and the ABCC in Hiroshima can be explained by differences in cell types of cancers of the colon lung and female genitourinary tract or by differences in treatment or duration of the terminal illnesses in the two countries. The contrasting incidences among neoplasms in the two sites cast doubt upon the concept that there is any real relationship between NBTE and specific tumors

The possibility has been raised that mucin production by tumors found in excessive frequency in association with NBTE may be etiologically related to the formation of verrucae upon valve surfaces This hypothesis has been related to a possible "hypercoagulable state conceived as an explanation for the general propensity for thrombus formation reported among cancer patients While many tumors found in the cases of the present study were of the cell types capable of mucin production no systematic histologic analysis has been made which can provide significant information on this question There was also no specific search made for lesions which might have indicated the presence of the disseminated intravascular coagulation syndrome

Pathogenesis of NBTE Any hypothesis concerning pathogenesis must be consistent with the rarity of the process in those dying in the younger age groups the evident association with chronic wasting disease primarily terminal cancer and the distinct predilection of these verrucae for specific sites on the left sided heart valves

One consideration is that NBTE may appear in relationship to those valve leaflet deformities known to be associated with aging Pomerance[17, 19] has published several analyses of the anatomy of cardiac valves in the elderly and in one study she has pointed out that after childhood a degree of nodularity appears along the line of closure of the atrial surface of the mitral valve almost certainly related to the impact of repeated closures of the valve However, such nodularity is present in all adult hearts and is no more apparent in the very elderly Another involutional change atheromatosis of mitral leaflets while clearly related to aging occurs ordinarily on the ventricular surface of the leaflets and is therefore an unlikely setting for NBTE [7] Both nodularity and atheromatosis appear primarily upon the anterior mitral cusp in contrast to the equal distribution of NBTE lesions between the two leaflets For the above reasons it appears unlikely that normal aging changes occurring in the mitral and aortic valves act as a major contributory factor in the appearance of NBTE in the elderly although the absence of involutionary leaflet changes in children may offer some explanation for the great rarity of NBTE among individuals of younger age groups dying of neoplastic and other wasting illnesses [5]

The microscopic appearance of the leaflet tissue described in this and other studies of NBTE closely resembles the lesions observed in experimental preparations of endocarditis following creation of arteriovenous shunts [2] In such animals the appearance of edematous valve connective tissue and loss of endothelial cells along the atrial closure surfaces of the leaflets is presumably associated in some way with either or

both the operative stress of the procedure itself and the high cardiac output state resulting from the shunt In another experimental study, Angrist and co workers[1] demonstrated similar valve lesions in rats subjected to a variety of stress procedures A later publication from the same laboratory further examined the biochemical changes associated with edema formation in valve tissue and indicated again that stress induced edema could be responsible for the valve distortion and exposure of collagen predisposing to thrombotic vegetations These lesions occurred to a greater extent in the left heart valves and in some instances nonbacterial thrombotic verrucae formed at the site of these lesions One cannot be certain that such histologic leaflet changes precede the appearance of verrucae in humans though it is our impression that this is the case A future analysis of cardiac valves in patients dying of disseminated cancer should reveal whether morphologic findings as described may indeed occur in the absence of verrucae

The missing link between the stress of a terminal illness associated with NBTE and the appearance of the leaflet tissue abnormalities is coupled with the absence of an explanation for the left sided predominance of the lesions Whereas Rodbard[23] has attempted to explain the left sided location of bacterial endocarditis as a result of high velocity flow and decreased lateral pressure accompanying pre existing valvular regurgitation or intravascular shunts, no such acquired or congenital defects are required for the appearance of NBTE on the mitral or aortic valves The almost complete absence of aging changes seen in adult tricuspid and pulmonary valves in contrast to the left sided valves[18] is almost certainly due to the much lower systolic and diastolic pressure levels to which the former are exposed This factor must also in some way explain the preponderance of the lesions of acute rheumatic inflammation bacterial endocarditis, and NBTE upon the aortic and mitral valves

Clinical implications of NBTE There is little doubt that embolization from NBTE can produce clinically apparent symptoms and signs and can add additional complications to the course of severe systemic diseases MacDonald and Robbins[3] and other authors have stressed the evidence of infarctions in many organs and in particular the clinical syndromes caused by emboli to the cerebral vasculature Of the 30 cases of NBTE reported by Bryan,[6] embolism was thought to be present in 22 and contributed to a fatal outcome in eleven instances Barron Siqueira, and Hirano [4] reported in an analysis of the association between NBTE and cerebral embolization that NBTE was present and perhaps the source of emboli in almost 10 per cent of their general autopsy series In a clinical pathologic discussion Adams [5] stressed not only that NBTE embolization may be the first clue to the presence of an occult carcinoma but also that, in his experience, a cerebrovascular episode in a patient with a malignant neoplasm may more likely be due to fragments from NBTE than to tumor embolization or metastases

A second important target organ of emboli from NBTE is the heart Coronary embolization with myocardial infarction, has been noted in several of the published series [6,8,15] and was seen in six cases of the present study It is conceivable that preterminal ischemic myocardial disease arrhythmias and cardiogenic shock may be the result of unrecognized coronary embolization from NBTE in more instances than suspected heretofore The appearance of focal myocytolysis in four cases in the present series associated in two cases with small intramural coronary artery thromboemboli, raises the possibility that embolic consequences of NBTE may be more frequently responsible for this particular form of myocardial lesion than has been appreciated

Although one might predict that valvular regurgitation due to leaflet displacement by verruca might lead to clinical suspicion of NBTE through the presence of cardiac murmurs this apparently is a rare accompaniment of NBTE Systolic murmurs are of course common in severe illnesses associated with anemia and fever and it would be difficult to attach greater significance to these auscultatory findings in such settings We are aware of only one reported case in which it seems quite certain that clinical awareness of a rapidly changing murmur was related to NBTE verruca preventing apposition of otherwise normal aortic valve leaflets [5]

Although NBTE may be considered by a physician when confronted by clinical clues such as described, a firm diagnosis of NBTE requires supporting laboratory confirmation An appropriate laboratory method may now be available in the form of echocardiographic techniques for Dillon and co workers[26] have recently reported

documentation of the presence of vegetations of bacterial endocarditis ranging from 2 to 8 mm in size in eight patients with subacute bacterial endocarditis (SBE) It should be possible to confirm the presence of nonbacterial vegetations in suspect cases by these same diagnostic techniques Such attempts may be aided by the fact that in at least some instances of NBTE the clinical picture of embolization and the organization of the verrucae noted at autopsy indicate that the process of NBTE has been a chronic one

Angrist and Oka[?] suggested that bacterial invasion of NBTE verrucae may produce the typical clinical and pathologic picture of bacterial endocarditis and that NBTE verrucae may actually represent healed bacterial endocarditis lesions Although it has been shown experimentally that bacterial infection of sterile valvular vegetations can be produced [?] MacDonald and Robbins have given cogent arguments against such a sequence linking bacterial and nonbacterial endocarditis in man In the present series also though a bacteriologic study had not been undertaken in any but a few instances the absence of any valvular abnormalities suggesting rheumatic heart disease and the minimal degree of cellular reaction in valve tissue makes any association between NBTE and bacterial endocarditis seem unlikely

In conclusion it is important that the possibility of NBTE be considered when in the setting of serious underlying systemic disease there is the sudden appearance of central nervous system signs or symptoms or clinical evidence consistent with embolic infarction of other organs primarily heart spleen and kidneys Such suspicion when coupled with echocardiographic techniques may permit more frequent diagnoses of NBTE in living patients and thereby permit studies directed at unraveling the mystery of the pathogenesis of this process

Summary

A study of nonbacterial thrombotic endocarditis has been carried out in a series of 3 404 autopsies performed upon atomic bomb survivors in Hiroshima in the period 1953 1970 The prevalence of the lesion was 2 4 per cent with a greater frequency among the elderly and among females and with a significant relationship to malignant neoplasms. In contrast to other reported series there was a greater prevalence among cancers of the colon rectum and female genitourinary tract No relationship was noted between the presence of NBTE and exposure to ionizing radiation

Histologic findings in the heart valve leaflets in close proximity to the verrucae like experimental studies reported by others suggest that in association with severe systemic disease there appears a process consisting of degenerative changes in valve collagen and ground substance with subsequent denudation of endothelium localized almost entirely to the apposing leaflet surfaces of the left heart valves The verrucae of nonbacterial thrombotic endocarditis are then formed upon this abnormal leaflet surface

While the relationship between systemic disease and the pathologic changes observed in cardiac valve tissue is unclear and although it is not known whether a hypercoagulable state may accentuate the tendency for thrombi to form upon these abnormal valves there is no doubt that this lesion represents a clinically important complication of severe systemic disease It also seems likely that in some cases NBTE may complicate an illness which may otherwise be curable

Increasing awareness of this pathologic entity among clinicians coupled with appropriate laboratory techniques most likely echocardiography will permit more frequent diagnosis in living patients

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Experimental and laboratory reports

Right atrium monophasic action potentials during atrial flutter and fibrillation in man

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The recording of monophasic action potentials (MAP s) from the intact human heart is a recently developed technique which may provide new data in the study of arrhythmias [1,2] It allows a more accurate detection of the electric activity of the underlying myocardium and permits correlation with experimental data utilizing intracellular electrodes [3] In former studies [4-6] the characteristics of right atrium MAP s in patients with atrial flutter and fibrillation have been described the onset course and termination of short paroxysms of atrial flutter and fibrillation were analyzed

The mechanism of atrial flutter and fibrillation has been a source of permanent interest for the cardiologist Circus movement theory versus repetitive stimuli from a single or more ectopic foci is a long lasting and unsolved controversy There is an agreement that atrial flutter and fibrillation are closely related arrhythmias and that their mechanism can be regarded as similar It was also stated that both rhythm disturbances can show different electrophysiologic patterns and mechanisms.[7]

From 52 patients with atrial flutter and fibrillation in whom MAP recordings were performed three examples were selected in which different types of electrical activity were simultaneously demonstrated by the technique The significance of these findings for the mechanism of arrhythmia and some common points between flutter and fibrillation are discussed

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Method

The method used in our laboratory has been reported previously [4] Bipolar suction electrode catheters passed percutaneously were utilized The catheter tip was placed under continuous monitoring in the right atrium its bore pushed gently against the endocardium and negative pressure was then applied with the aid of a simple suction device For electrophysiologic studies a second bipolar pacing electrode was located in the right atrium A specially constructed battery powered pulse generator[8] was used for atrial pacing

Results

Patient No 1 The surface electrocardiogram showed atrial flutter of the common type The flutter waves were predominantly negative in Leads II III and aV_F and had a rate of 266 per minute There was a 3 1 A V conduction and QRS axis was at 0°

MAP recorded from the high right atrium shows the typical pattern of atrial flutter (Fig 1 A) The MAP complexes had a cycle length of 225 msec identical with those of the flutter waves on surface electrocardiogram This pattern was also recorded in the rest of the right atrium with the exception of its lower part where a different type of electric activity was recorded (Fig 1 B) Two MAP complexes with a distance of 90 msec between them were observed for each flutter wave seen in the first tracing and surface electrocardiogram

An attempt to stop the flutter with the aid of atrial pacing using a stimulation rate lower than atrial rhythm was unsuccessful Rapid atrial pacing at a rate of 400 per minute with paired stimuli (S_1 S_2 20 *msec*) captured the atria (Fig 2 A) for 20 seconds then the pacemaker was turned

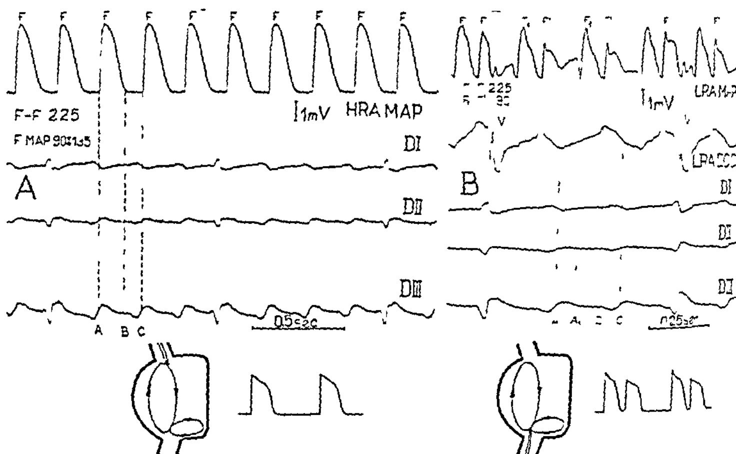


Fig 1 Patient 1 *A* MAP *recording from the high right atrium (HRA MAP) simultaneously with Leads I II and III There is regular atrial activity at a rate of 226 per minute Paper speed 100 mm per minute F F cycle length F MAP 90 per cent MAP duration in milliseconds of the flutter waves measured at 90 per cent of amplitude B* MAP *recording from the low right atrium (LRA MAP) simultaneously with an intra atrial electrogram (LRA ECG) and Leads I II and III Paper speed 200 mm per second F and F are MAP complexes recorded for each flutter wave* The vertical dotted lines show the relation between MAP records and flutter waves on surface electrocardiogram The diagrams depict the proposed explanation of the MAP recordings according to the position of the exploring electrode

off Rapid atrial activity showing the same rate as during pacing ensued and persisted for several minutes During this period the surface electro cardiogram showed a pattern of atrial fibrillation with ample f waves and aberrant ventricular conduction (Fig 2, *B*) The transition from atrial fibrillation to flutter with its initial characteristics is shown in Fig 2, *B* There is a sudden change in the cycle length of atrial activity from 150 to 220 msec This change takes place with slight variations of MAP complexes On the other part, the surface electrocardiogram returns to its initial configuration only after the tenth flutter complex It can be supposed that during this period the atrial wall had a nonuniform activity

Patient No 2 This patient had atrial flutter of the common type with an atrial rate of 300 per minute Flutter waves were negative in Leads II III, and aV_F A V conduction was 2 1 and 3 1 The ventricular complexes had an QRS axis at −60° Fig 3 shows an intra atrial electrogram recorded in the lower part of the right atrium with two separate deflections for each flutter wave The distance between these deflections was 80 msec

Patient No 3 Surface electrocardiogram revealed atrial fibrillation with large f waves, irregular ventricular activity and a QRS axis at +60° MAP recordings from a limited zone of the high right atrium disclosed a regular atrial activity, at a rate of 180 per minute, showing large MAP complexes with a duration of 180 to 200 msec, very similar to those seen during atrial flutter (Fig 4, *A*) An entirely different type of electric activity was recorded in the lower parts of the atrium There was a rapid rate of about 400 per minute and small irregular complexes typical for

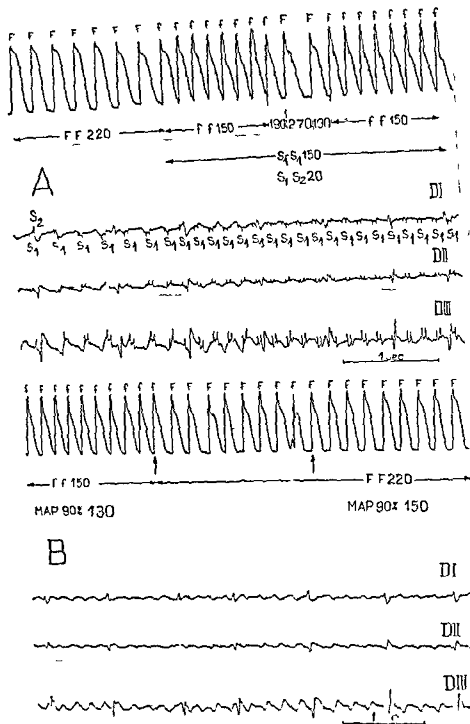


Fig 2 Patient 1 *A* MAP recording *from the* high right atrium during paired pacing (S S ?0 msec) From the ninth MAP complex the atrium is stimulated with a rate of 400 per *minute* An ineffective stimulus is seen at the sixteenth and *seventeenth* MAP complexes, allowing the occurrence of flutter mechanism F F = cycle length of flutter waves, f f = cycle length on stimulated complexes (milliseconds) *B* After cessation of pacing rapid atrial activity at a rate of 400 per minute is seen at the beginning of the tracing First arrow pointed up shows transition from fibrillation to flutter on MAP recording Second arrow pointed up marks the return to initial atrial flutter on surface electrocardiogram MAP 90 per cent indicates the duration of monophasic action potentials in milliseconds measured at 90 per cent of its amplitude

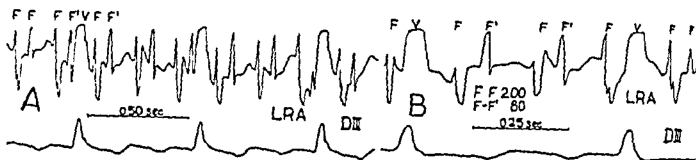


Fig 3 Patient 2 Intra atrial electrogram recorded simultaneously with Lead III in low right atrium (LRA) showing two deflections (F F) for each flutter wave Left panel paper speed 100 mm per minute Right panel, paper speed 200 mm per minute

atrial fibrillation (Fig 4, *C*) An intermediate pattern was recorded in the middle of the atrium where large and small MAP complexes could be seen (Fig 4 *B*)

Discussion

The purpose of this paper was to underline some characteristics of the atrial depolarization during atrial flutter and fibrillation Some features of atrial flutter indicate that this arrhythmia may be due to a re entry circuit established within the atrial tissue [10] Other data are pleading for the existence of an ectopic focus located low in the atrium or upper part of the A V node [11] [12] Studies based on the form of flutter waves expressed the view that in the majority of clinical cases of atrial flutter of the common type the impulses are formed in the caudal end of the atria [13] [14] Kishon and Smith[7] utilizing intra atrial and esophageal records in patients with atrial flutter demonstrated an activation pattern which was thought to be compatible with the circus movement theory In other cases activation was believed to originate low in the atrium with simultaneous spread of excitation of both atrial walls in a general cephalad direction a pattern compatible with an ectopic focus The presence of two deflections for a flutter wave in an esophageal tracing was considered by Prinzmetal and co workers[13] as evidence for the circus movement theory such deflections were seen in intra atrial electrograms in some of the cases studied by Kishon and Smith [7] It was supposed that if the exploring electrode is incidentally placed symmetrically in regard to the excitation pathway i e, the re entry circuit, a pattern showing two separate deflections for each wave could be recorded In our patients a limited zone in the lower part of the right atrium was found where two MAP complexes were recorded for each flutter wave

Although MAP recordings do not permit an evaluation of the activation spread in the atrial wall but only the voltage time course the presence of the two atrial depolarizations can be explained by the activation pattern of the atrium If the assumption that the MAP represents an action potential is correct,[3] then in the low right atrium two atrial depolarizations were recorded for each flutter wave This may be due to the fact that the electrode tip was placed incidentally in the area of re entry a limited zone of the atrial myocardium or on a segment of the main re entry circuit where the excitation reactivates the atrial wall In this case the circus movement of the flutter wave can show the configuration of the diagrams of Figs 1 and 4 the intersection of loops taking place in the lower part of the right atrium

An alternative explanation is that in the lower parts of the right atrium the exploring electrode was incidentally placed in an area where the activations of the right and left atria were recorded separately This assumption is not likely because the MAP recorded at the tip of the electrode represents the depolarization and repolarization phenomena in a very limited area of the myocardium [4]

The effect of rapid atrial pacing in patient No 1 also deserves some comments Atrial flutter was changed into atrial fibrillation after 20 seconds of pacing In the first seconds when occasionally, a stimulus was ineffective (Fig 2, *A*) the flutter mechanism occurred again It was necessary to stimulate the atrium for about 20 seconds to induce atrial fibrillation Atrial activity recorded after cessation of pacing had a rate of 400 per minute identical to that used during stimulation It is questionable whether a rapid firing focus was induced during pacing or the excitation pathway of the circus movement has been deviated on a

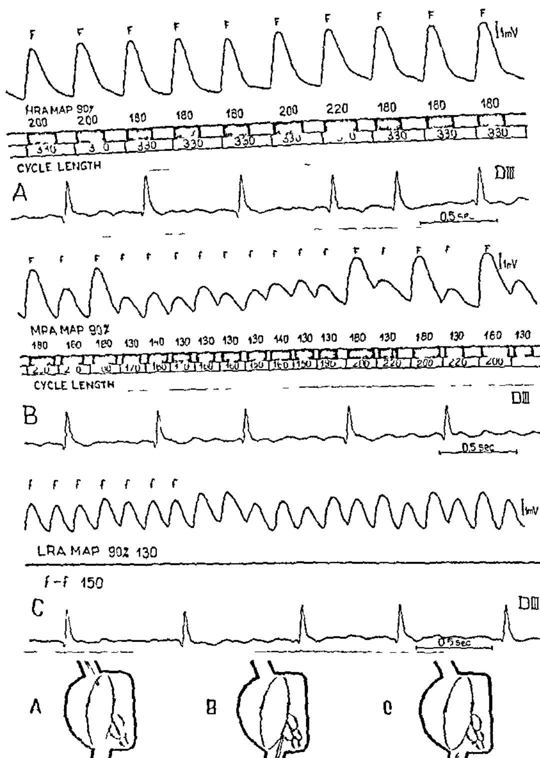


Fig 4 Patient 3. *A* MAP recording simultaneously with *Lead III* in the high right atrium (HRA MAP) showing regular activity at a rate of 180 per minute MAP duration (black spaces) and cycle length (white spaces) are given in milliseconds for each complex *B* MAP recording in the middle right atrium (MRA MAP) *C* MAP recording in the low right atrium f f is the cycle interval in milliseconds. The diagrams show the proposed explanation for recordings *A B* and *C* according to the position of the exploring electrode in respect to the main re-entry circuit and daughter waves.

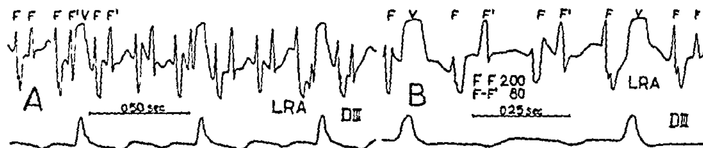


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shorter route[15] We think that the first explanation is more likely, because after a short time the atrial activity returned to its initial mechanism The transition from fibrillation to flutter took place suddenly without any progressive prolongation of MAP complexes as seen during the spontaneous conversion to sinus rhythm of atrial fibrillation induced experimentally by a stimulus falling in the vulnerable period of the atria[16] On the other hand on surface electrocardiogram flutter waves appear after only two seconds It is possible that during this interval the atrial wall activity was not uniform Patient No 1 illustrates the possibility of an arrhythmia due to circus movement (atrial flutter) to change into atrial fibrillation induced probably by a rapid firing focus

In patient No 3 three different types of atrial activity could be recorded a slower regular activity showing marked resemblances to flutter with a rate of 180 per minute a rapid irregular activity with a rate of 400 per minute and a mixed type We suppose that in this patient the exploring electrode has been placed incidentally in areas activated by the main re entrant circuit (mother wave) then in areas where the development of multiple sites of re entrant activity and fractionation of wave front into many wavelets has taken place Atrial dissociation[17,18] can also explain the presence of two different rhythms simultaneously activating the atria Unilateral atrial flutter and fibrillation have been described[17,19] however a diagnosis of atrial dissociation becomes extremely difficult when two ectopic rhythms co exist The presence in our case of a mixed type of atrial activity with large and small MAP complexes recorded at the tip of the exploring electrode is an argument against the presence of two different completely independent atrial rhythms without any interference between them

In the examples of atrial flutter and fibrillation presented above the electric activity of the right atrial wall was nonuniform In each of the two patients with atrial flutter there was a site which showed two separate action potential deflections for each flutter wave This area permits the recording of MAP complexes with the characteristics of those found during atrial fibrillation This phenomenon was thought to express an area of re entry In the patient with atrial fibrillation a small area of the right atrium showed an electrical activity characterized by large waves with a rate of 180 per minute showing marked resemblance to the flutter waves In the rest of the atrium the typical irregular activity of atrial fibrillation, with a rate of 400 per minute was observed There was no evident correlation between the two rates recorded in the atrium it is possible that these differences are due to the distance traveled by the excitatory processes (mother wave and daughter waves)

The characteristics of atrial depolarization during atrial flutter and fibrillation may explain the close similarity between the fundamental mechanism of both arrhythmias which may change frequently one into the other It is also possible that, due to particular circumstances a re entry circuit may change into a rapid firing focus and inversely

Summary

Monophasic action potentials recorded in two patients with atrial flutter and one patient with atrial fibrillation showed a nonuniform depolarization of the right atrial wall In each of the two patients with atrial flutter, there was a site where two separate action potential deflections were recorded for each flutter wave It was supposed that this was the site of re entry for a cycling wavelet subsidiary to the main flutter wave In the patient with atrial fibrillation three types of electric atrial activity were found regular activity at 180 per minute similar to that found in flutter small irregular activity at a rate of 400 per minute and a mixed type of the former two The significance of these findings for the mechanism of atrial flutter and fibrillation is discussed

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Studies on the experimental production of endomyocardial fibrosis and cardiomegaly of unknown origin by dietary means

Brian McKinney D Sc , M D , M R C Path
London England

Cardiac lesions similar to those found in cardiomegaly of unknown origin (CUO) have been produced by dietary means in rats fed on tryptophan deficient diets similar to those eaten by many of the indigenous people in areas where this disease occurs [1]

Endocardial and myocardial lesions which appear, although to a lesser extent, to resemble those of endomyocardial fibrosis (EMF) have been produced in guinea pigs fed on a diet consisting largely of plantains [2]

Plantains are eaten as the principal dietary staple in those regions where EMF is found This diet is tryptophan deficient[3] but contains a large quantity of 5 hydroxytryptamine (5 HT) which has a 'protective' action on the myocardium [4]

Spatz[5] later extended and substantiated these observations by (1) using tryptophan deficient diets and (2) in some animals administering additional amounts of 5 HT This has produced lesions similar to those of CUO and EMF

This work was extended in a long term study in which rats were given diets similar to those eaten in areas where EMF and CUO are commonly found

A diet low in protein and other essential nutrients[6] may possibly be of importance in the development of EMF as it is known that individuals, such as the Banyaruanda in Uganda who exist on a high plantain and high-carbohydrate diet, containing only a small amount of protein and other essential nutrients, have a high incidence of EMF

The better off Baganda who, although eating a high carbohydrate diet which consists largely of plantain, also have an adequate protein intake, rarely develop EMF

It was therefore also decided to investigate whether a high protein intake would prevent the development of EMF in rats being fed a plantain diet

Methods

Sixty weanling Sprague Dawley rats were divided into three groups of 20 animals Each group was placed on one of the three diets described in Table I

These animals were then kept on these diets for periods ranging from 15 to 30 months before being killed The mothers of all these rats had previously been kept on the particular type of diet under study since first becoming pregnant

Casein gives a good balance of amino acids. Therefore gelatine is used because it is tryptophan deficient and creates an imbalance of essential amino acids Although a low protein diet suppresses growth rate it has been shown experimentally that an imbalance of essential amino acids has a more profound effect [7]

The hearts were removed and examined macroscopically Transverse blocks through both ventricles and the interventricular septum were then cut, doubly embedded, sectioned at 5μ, stained, and then examined microscopically

The stains used were hematoxylin and eosin

From the Department of Pathology The Royal Free Hospital London England

The expenses of this study were covered by a grant from Smith Kline & French The Wellcome Trust provided personal financial support for the author while this study was being carried out A grant from the British Heart Foundation paid for the Vickers Patholux microscope with which the histological material was examined and photographed

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Alcian Blue to demonstrate acid mucopolysaccharides, Martius Scarlet Blue for fibrin and Verhoef-Van Giesen for elastic tissue

Results

The 'maize and plantain diets—diets A and B—resulted in the appearance of cardiac lesions after about 15 months and lesions were most marked in animals who had been kept on those diets for up to 30 months Those rats on the high protein diet—diet C—did not develop any significant cardiac lesions.

Rats which died before having been on the diet for 6 months or more were excluded from consideration as there had not been time for cardiac lesions to develop These and losses by cannibalization (four instances) account for the discrepancy between the number of rats placed on diets and the number of hearts examined Causes of the early deaths were pneumonia and pyelitis

Table II shows the distribution of heart weights found at death in the rats in the three dietary groups. The mean and median values for each group are also given There is a considerable difference between the heart weights in Group A animals (low tryptophan diet) and those in Groups B (plantain diet) and C (plantain diet supplemented by a high protein intake) This difference is statistically significant ($p < 0.001$) There is no significant difference between the heart weights in the animals in Groups B and C

The cardiac lesions found microscopically in these animals are shown histogrammatically in Figs. 1 and 2 In this study ± + or ++ mean that the lesion is mild moderate or severe In constructing the histograms these lesions were given values of 1 2 or 3 so that the maximum value for any one lesion was 45 (100 per cent)

Group A

Macroscopic examination. The affected hearts were enlarged by both dilation and hypertrophy up to three times their normal weight (1,200 mg) Both ventricles were equally affected but the atria much less so although there was an occasional adherent thrombus in the atrial cavity

The ventricular endocardium presented a range of appearances from normal to severely affected In these latter cases it had an opaque white appearance and the trabeculae carneae sometimes became thin white fibrous cords These changes seemed to be more commonly seen in the left than in the right ventricles and then only microscopically and to a much lesser degree than in those lesions on the left side

Other postmortem findings in affected rats were chronic venous congestion of many organs secondary to heart failure and sometimes pulmonary or cerebral infarctions

Microscopic examination When present the endocardial lesions usually consisted of a thin layer of fibrous tissue laid down over the endocardium (Fig 3) Sometimes the layer was much thicker and could be seen macroscopically

When stained with elastic tissue stains either Orcein or Van Giesen the endocardium was often seen to contain many elastic tissue fibers (Fig 4)

The more superficial parts of the thickened endocardium did not usually contain any elastic tissue fibers (Fig 5) The endocardium stained well with Alcian Blue and showed the presence of much acid mucopolysaccharide

Toluidine blue staining did not reveal any metachromasia in the endothelial cells.

When stained by the Martius Scarlet Blue technique a thin layer of fibrin directly overlying the endocardium (Fig 6) was often present The

Table I Composition of diets A B and C

Diet A—"maize"		*Diet B—low protein and high carbohydrate (plantain)*		*Diet C—high protein and plantain*	
Cooked maize	36.0%	Plantain	90%	Plantain	60%
Sucrose	3.5%	Casein gelatine mixture	6%	Soybean oil	10%
Beans	32.0%	Minerals and vitamins	4%	Casein	25%
Sour milk	27 0%			Minerals and vitamins	5%
Salt	1.5%				

Table II Distribution of heart weights of rats on diets A B and C

	Heart weight at death (mg)		
	Diet A	*Diet B*	*Diet C*
Distribution	0 7"5-3 334	0.906-2.239	0 606-? 045
Mean	1 793	1 490	1.267
Median	1.577	1 477	1.213

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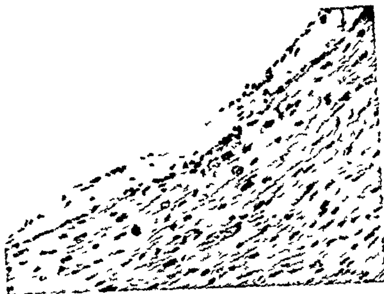


Fig 3 Showing the slightly thickened endocardium which is often present in those rats which have been kept on a maize —Group A—diet. Rat 1A (Hematoxylin and eosin ×80)



Fig 4 Showing thickened endocardium which contains many fine elastic tissue fibers Rat 1A "maize" diet. (Orcein Van Gieson ×80)



Fig 5 Showing the thickened endocardium in a rat which has been on a "maize" diet—Group A—the more superficial parts of which contain no elastic tissue

In general the fibrosis was more severe in the left ventricle and in the inner subendocardial part of the myocardium

The myocardial fibers had in places lost their normal cross striations but this may have been an artifact (Fig 9) some of the nuclei were pyknotic and distorted in shape and sometimes individual cells did not take up eosin to any marked degree (Fig 10) When these sections were stained with cresyl violet some of the cells were found to contain fuchsinophilic material an early sign of myocardial damage

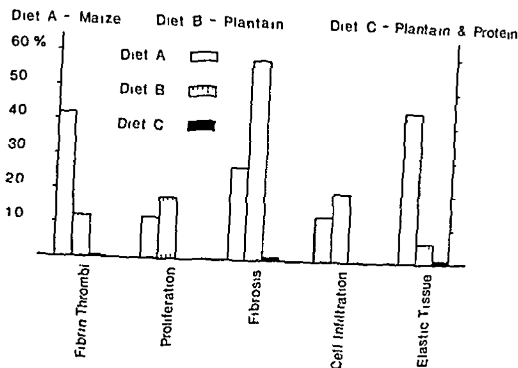


Fig 1 Histogram to show the incidence of pathological changes produced in the cardiac endocardium of rats on the different diets used in this study

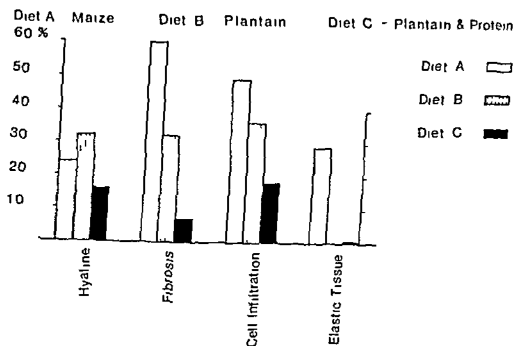


Fig 2 Histograms showing the incidence of pathological changes found in the myocardium in rats fed on the different types of diet used in this study

endocardium itself did not usually contain any deposits of fibrin

The ventricular myocardium showed some interstitial edema and usually areas of interstitial fibrosis (Fig 7) This fibrosis may form small areas around small intramyocardial blood vessels There was some variation in myocardial fiber size but hypertrophy of myocardial fibers could not be demonstrated with any degree of certainty

This fibrosis, when present often formed a thin layer of collagen passing between the muscle fibers

Sometimes the endocardium was considerably thickened by fibrous tissue which extended into and replaced the more superficial myocardial cells The deeper parts of the thickened endocardium contained numerous thin walled and congested blood vessels (Fig 8)

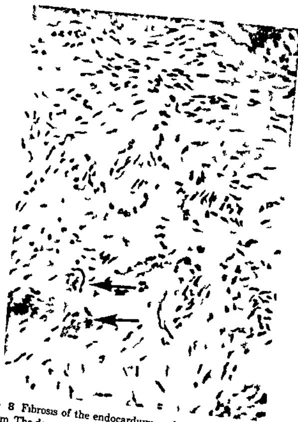


Fig 8 Fibrosis of the endocardium and underlying myocardium The deeper parts of the thickened endocardium contain several thin walled dilated and congested blood vessels (arrowed) Rat 1A maize diet (Hematoxylin and eosin ×80)

endocardium in most parts of the atria and in the inflow tracts and apices of the ventricles were often slightly thickened but that of the outflow tracts was normal This endocardial thickening was usually only a few cells in width together with a few collagen fibers

Often though no endocardial thickening was present there was a thick layer of myocardial tissue which had lost its normal striations and had assumed a hyaline appearance

Sometimes particularly on the inflow side of the left ventricle and at the ventricular apices this thickening was more marked (Fig 11) The thickened endocardium when stained with Orcein or Van Giesen stains did not reveal the presence of any elastic tissue except for a few fibers at its base which appear to be part of the basement elastic tissue of the original endocardium (Fig 12)

Martius Scarlet Blue stain for fibrin sometimes showed small amounts of fibrin lying on the surface of the endocardium (Fig 13) Sometimes these small deposits were seen to be undergoing

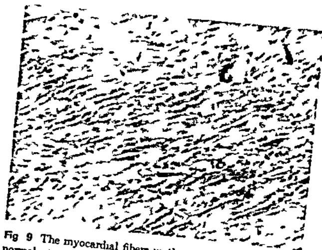


Fig 9 The myocardial fibers in this section have lost their normal, striated appearances. There is also a diffuse infiltration with small lymphocytes Rat 1A "maize" diet—Group A (Hematoxylin and eosin ×80)

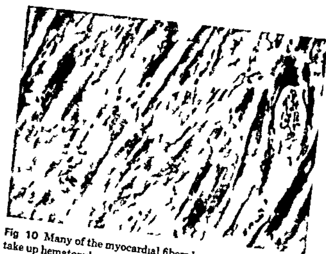


Fig 10 Many of the myocardial fibers have lost the ability to take up hematoxylin and eosin the cells often appearing to be necrotic and sometimes to be replaced by fibrous tissue Rat 1A maize diet (Hematoxylin and eosin ×80)

organization especially when connected with an overlying thrombus

The underlying myocardium was often normal the myocardial cells did not show evidence of hypertrophy The nuclei of many of these cells were normal but others often showed some degree of pyknosis or contained abnormally shaped nuclei such as those resembling a stag s horn

In some areas these myocardial cells had lost the striated appearances of their cytoplasm and had become hyaline in appearance

Sometimes these cells had small vacuoles within their cytoplasm and had lost their normal ability to take up eosin so that these myocardial cells appeared as faint shapes

There was often a diffuse infiltration of the

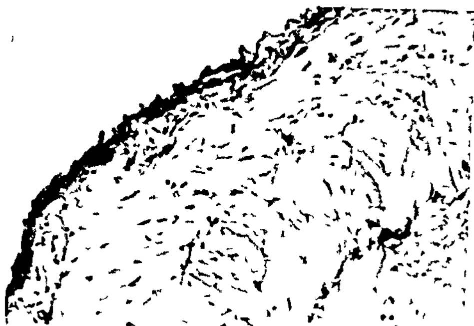


Fig 6 Showing a thin layer of fibrin overlying a slightly thickened endocardium Rat 1A 'maize diet. (Martius Scarlet Blue ×80)



Fig 7 This shows a small area of fibrosis within the myocardium on the left of the picture the fibrosis extends around a small intramyocardial blood vessel Rat 1A maize diet—Group A (Hematoxylin and eosin ×80)

Toluidine blue staining did not reveal any metachromasia in the endothelial cells

In some parts of the myocardium there were slight infiltrations with small lymphocytes being in some places aggregated into distinct foci but in these cases there was no associated damage to the underlying myocardium

Apart from congestive changes, microscopic study of other tissues showed only occasional nonspecific changes such as fatty infiltration of the liver or mild hepatic fibrosis and acute or chronic pyelonephritis The tissues which were routinely examined were the liver, pancreas spleen and kidney

Ten of the 15 rats in Group A (tryptophan deficient "maize' diets) showed some evidence of myocardial fibrosis

The hearts of the five animals which did not show fibrosis were not, however, normal This is shown by the finding that most were heavier than those of normal rats of the same age Plasma levels of tryptophan or tryptophan content of tissues in these animals were not determined as no facilities were available for this study

Group B

Macroscopic examination Macroscopically some of these hearts were slightly larger than normal but there was no statistically significant difference between their weights and the hearts of those animals which had been on a plantain and high protein diet Externally these hearts appeared normal although in many of the animals examined there was a pericardial effusion of clear colorless fluid

Many hearts were slightly dilated on opening, particularly the atria The endocardium was often slightly thickened, particularly toward the ventricular apices and in the inflow tracts Small thrombi were often present within the atria or ventricles Sometimes these thrombi were becoming incorporated by a process of organization with adjacent areas of the endocardium so that they were adherent to the underlying cardiac tissue

These lesions in the hearts are shown in Figs 1 and 2

Microscopic examination Microscopically the



Fig 14 The endocardium is not thickened and the myocardium is normal in appearance Rat 2C "plantain diet supplemented by a high protein intake (Hematoxylin and eosin ×80)

and at autopsy no abnormalities were seen in either the heart or the rest of the body These changes are shown in Fig 2

Microscopic examination The endocardium and myocardium were normal (Fig 14) Two animals showed evidence of chronic pyelonephritis but no evidence of thromboembolic episodes was seen These animals were all normal and neither their hearts nor any other parts of their cardiovascular systems revealed abnormalities

Discussion

This study has shown the following results First in those animals which have been on the maize diet (Group A) of the type eaten by many indigenous inhabitants of Africa cardiac lesions were produced similar to those found in cases of CUO This confirms the results obtained by Reid and Berjak[1] using a similar type of tryptophan deficient diet

The rats in Group B had been on a plantain diet which was also markedly tryptophan deficient but also contained a large amount of 5 HT In these animals there was often as much endocardial thickening as in the Group A animals—or more—but there was usually no or very little elastic tissue in the thickened endocardium Other points of difference from Group A animals are that there was considerably less myocardial fibrosis or lymphocytic infiltration of the myocardium and that superficial deposits of fibrin were seen more commonly in Group A animals This pathological picture very closely approximates to that seen in EMF

Group C animals were fed on a diet which consisted largely of plantain but also contained a high protein content to ensure that the diet was not tryptophan deficient In none of these animals were any cardiac lesions found This high protein diet probably explains why the Baganda in Uganda who eat a diet containing a large amount of plantains do not develop EMF whereas the Banyaruanda who are generally undernourished and eat little or no meat or other protein rich foods but consume a large amount of plantain do

That the lesions of EMF produced in the Group B animals differ so widely from the lesions of CUO produced in the Group A animals may be due to the protective action of 5 HT on the myocardium in the sense of accounting for the less damaging changes (EMF) in Group B animals compared with the greater damage (CUO) in the tryptophan deficient nonprotected Group A animals as postulated by Spatz[4]

These results explain the etiology and development of CUO in tryptophan-deficient diets but do not explain how EMF may develop in people who are living on a normal diet although they have in the past consumed large amounts of plantain These findings have often been put forward to demonstrate that EMF cannot have a dietary origin

It has lately been shown that in cases of carcinoid heart disease where the initiating factor is thought to be 5 HT the disease may continue to progress although the original carcinoid tumors (the source of 5 HT) have been completely removed[5]

The evidence that 5 HT or associated compounds must be the etiological cause for the

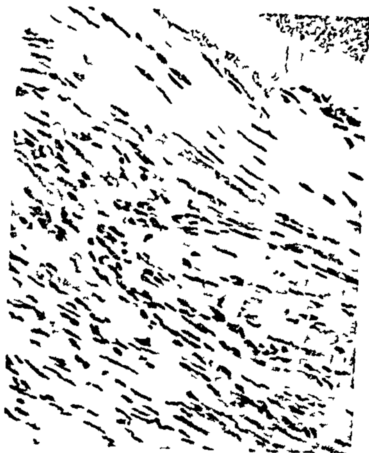


Fig 11 The endocardium is thickened beneath it there is a cellular infiltrate of the myocardium Rat 2B plantain diet (Hematoxylin and eosin ×80)



Fig 13 Showing thickened endocardium which is overlain by a layer of fibrin Numerous small threads of fibrin are also present within the thickened endocardium Rat heart 1A maize" diet (Martius Scarlet Blue ×80)



Fig 12 Showing that the thickened endocardium contains no elastic tissue Rat B5 plantain" diet (Verhoef-Van Gieson ×80)

myocardium with lymphocytes which were also sometimes found in small foci, particularly around small blood vessels

Some strands of fibrous tissue pass down into the myocardium from the overlying endocardium but elsewhere there were small foci of fibrosis within the myocardium

The intramyocardial blood vessels were congested and dilated They were normal except that they might be surrounded by a zone of perivascular fibrosis

The *pericardium* is usually normal except that there may be a slight infiltration with lymphocytes

In the remainder of the body, apart from changes due to congestive heart failure no changes were seen of pulmonary or systemic infarction but in a few cases evidence of pneumonia or pyelitis was present

Group C

Macroscopic examination The hearts in these animals were all of *normal size None* showed evidence of congestive heart failure The majority of these animals had lived perfectly normal lives

The superior QRS axis in ostium primum ASD
A proposed mechanism

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A superior mean QRS axis (AQRS) is characteristic of certain congenital cardiac malformations especially defects involving the endocardial cushions The pathophysiology of the abnormal axis in this anomaly has been ascribed by several authors to a left anterior hemiblock [1 3] Although there is sufficient pathological and clinical evidence to believe that a superior AQRS seen after surgery in some patients with a ventricular septal defect [2 4] tetralogy of Fallot [6] or degenerative heart disease[7] is due to a left anterior hemiblock there is as yet a lack of conclusive evidence to suggest that this is the mechanism of the superior AQRS in ostium primum atrial septal defect (OPSD)

This study was undertaken to elucidate the mechanism of the superior ÂQRS in OPSD and to distinguish it from left anterior hemiblock This was done by demonstrating the effects of abnormal hemodynamics ventricular hypertrophy and right bundle branch block (RBBB) on the superior AQRS Furthermore the natural history of patients with OPSD and RBBB was compared with that of those patients exhibiting true bifascicular block The results indicate an alternate mechanism for the superior AQRS in this malformation other than left anterior hemiblock.

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Rece ed f publicat May 23, 1974

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Material and methods

Twenty nine patients (11 males and 18 females) with a surgically confirmed diagnosis of OPSD formed the basis of this investigation Excluded from the study were patients who (1) had Down s syndrome (2) failed to survive the immediate postoperative period (3) had a complete atrioventricular (A V) canal or additional significant malformations (4) were older than 25 years of age at the time of surgery or (5) had inadequate pre and postoperative electrocardiograms (ECG) The age at surgery ranged from 3 6 to 24 3 years (mean 11 years) The follow up period since surgery has been from 12 days to 14 5 years (mean 4 4 years)

The last preoperative and most recent postoperative ECG in all 29 patients were utilized for analysis ECG s were recorded in a conventional fashion at 25 mm per second with full standardization The AQRS was computed empirically with a hexagonal frontal plane reference frame[10] and the areas and magnitudes of two or more standard or augmented limb leads Ventricular hypertrophy was diagnosed according to the ECG criteria established in the Harriet Lane Handbook Right bundle branch block (RBBB) was diagnosed when a terminal conduction delay produced a QRS duration in excess of or equal to 120 msec A superior AQRS was defined as being less than 330 degrees with at least an initial counterclockwise inscription in the frontal plane

Vectorcardiograms (VCG) recorded in the Frank lead system were available preoperatively in 16 patients and postoperatively in 7 of the 16 These were analyzed for the mean QRS vector as

cardiac lesions in the carcinoid syndrome and could be a factor in EMF from plantain consumption is derived from the following observation

Parachlorophenylalanine is a powerful depleter of tissue serotonin (5 HT) and it was thought that many of the side effects could be eliminated by long term therapy with this agent However in the above two cases of Trell and associates[8] this was not found In one of these patients the serotonin levels were kept normal for 8 months by PCPA but the tricuspid incompetence increased These investigators concluded that serotonin might not be the cause of the carcinoid lesions An alternative interpretation may be that cardiac lesions, once established, may be self perpetuating leading to further progression despite elimination of the original biochemical factors

Similar results were found by Satterlee, Serpiek and Bianchine[9] who found that PCPA when used in treating the carcinoid syndrome promptly reduced 5 HT levels to normal and stopped the diarrhea but did not prevent tumor growth, flushing attacks, or the progression of cardiac lesions In these cases the right sided cardiac lesions appeared clinically to progress This suggests that the fibrotic cardiac lesions may progress significantly even though the concentration of circulatory 5 HT is within normal limits Other factors or 'co factors' may be responsible for these fibrosing lesions[10] The response of the myocardium and endocardium to different insults may be limited and different factors could produce a similar end result However the evidence here coupled with the low socioeconomic predominance of EMF strengthens the case for a dietary role in its etiology

Summary

Three groups of rats were kept on diets similar to those eaten by indigenous inhabitants in parts of Africa where CUO and EMF are commonly found, for 30 months

Many of the animals on a tryptophan deficient diet developed CUO whereas those on a tryptophan deficient diet which contained a 5 HT content also developed lesions similar to EMF The third group of rats, which ate a diet similar to this second group but supplemented by a high protein intake, did not develop any cardiac lesions

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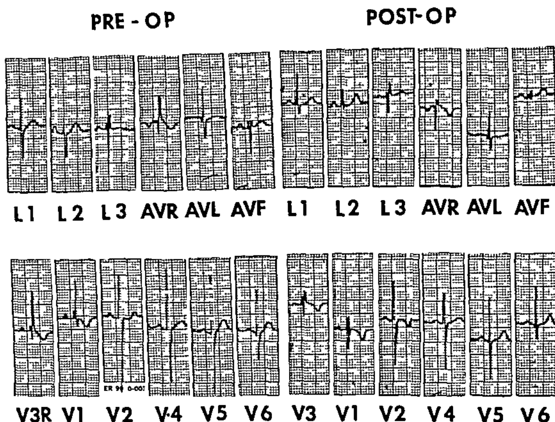


Fig 4 Typical decline in the AQRS following postoperative resolution of RVH

strated a right ventricular pressure of 43 mm Hg and a pulmonary systemic flow ratio of 3 4 1 He had a AQRS of 350 degrees and ECG criteria for only left ventricular hypertrophy (LVH)

Postoperative cardiac catheterizations were performed on 11 of the 23 patients and in all of them closure of the defect was confirmed by indicator dye dilution technique Although in most cases there was persistent ECG evidence of right ventricular hypertrophy (RVH) the AQRS became less superior by a mean of 20 degrees whereas the RV pressure diminished to normal levels Exceptions were two patients with RBBB incurred at operation

ECG The preoperative AQRS was examined with respect to chamber hypertrophy In 20 patients with criteria for right or biventricular hypertrophy (BVH) the mean AQRS was 290 degrees (Fig 2) seven patients with isolated left or no ventricular hypertrophy had a mean ÂQRS of 310 degrees two were normal

The AQRS of 10 patients who had RVH or BVH preoperatively and no ventricular hypertrophy postoperatively are shown in Fig 3 With the resolution of ventricular hypertrophy there was a significant shift in the AQRS from a mean of 290 to 330 degrees postoperatively The AQRS in three of the original 10 patients returned to within normal limits Fig 4 is an example of a patient in whom the diminution of the superior AQRS occurred with the resolution of RVH postoperatively Patients who had persistent evidence of ventricular hypertrophy postoperatively had no significant change in their AQRS These findings suggested that the AQRS was dependent upon the presence of RVH or BVH for *its* superiorness and that the abolition of hypertrophy shifted the AQRS toward the normal range

Two patients satisfied the criteria for RBBB preoperatively Their AQRS did not change postoperatively Another two patients who had evidence for RVH preoperatively incurred RBBB at the time of surgery A more superior and rightward ÂQRS resulted with the induction of RBBB (Fig 5)

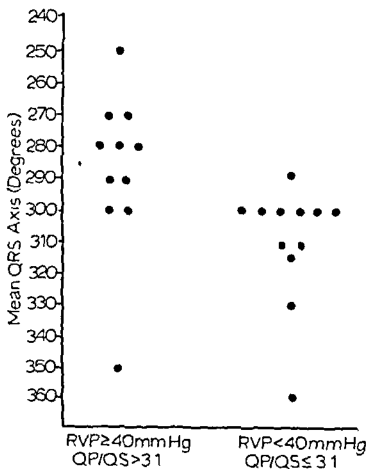


Fig 1 With RVP ≥ 40 mm Hg or pulmonary systemic flow ratio (QP/QS) greater than 3 1 the mean QRS axis was 285 it was 310 with a pressure or shunt ratio below these levels (dashed line represents mean)

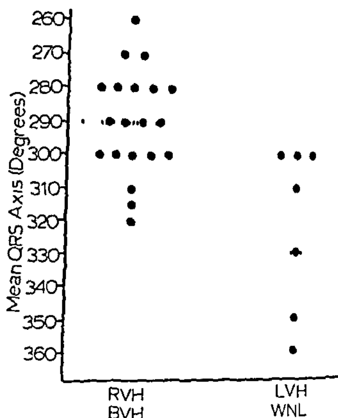


Fig 2 The mean QRS axis with either RVH or BVH was 290° Patients with LVH or no hypertrophy had a mean axis of 310° (dashed line represents mean)

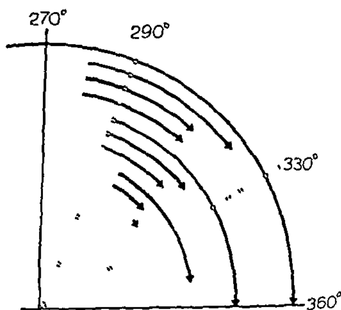


Fig 3 Postoperatively the superior AQRS declined from a mean of 290 to 330 following resolution of ventricular hypertrophy

outlined by Chou and Helm [12] The time at which the frontal plane loop first became superior divided by the total QRS duration represented the proportion of time the loop remained inferior When this quotient was subtracted from one the proportion of time the loop remained superior was obtained

Hemodynamic data were available in 23 patients preoperatively and in 11 of the 23 post operatively Pulmonary systemic flow ratios were computed based on the Fick principle and the presence or absence of a shunt by indicator dye dilution techniques

Results

Hemodynamic data In 23 patients preopera tive cardiac catheterization data were correlated with the ÂQRS of ECG's taken at approximately the same time as the procedure Patients with either a right ventricular pressure (RVP) greater than or equal to 40 mm Hg or a pulmonary sys temic flow ratio greater than 3 1 had an abnor mally superior AQRS less than or equal to 300 degrees (mean 285 degrees) (Fig 1) On the other hand, those patients who had right ventricular pressure less than 40 mm Hg or a pulmonary sys temic flow ratio less than or equal to 3 1 generally had a AQRS greater than or equal to 300 degrees (mean 310 degrees) The exception was a 10 year old boy who at cardiac catheterization demon

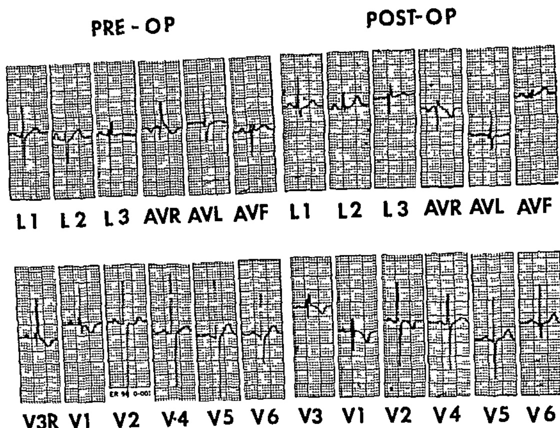


Fig 4 Typical decline in the AQRS following postoperative resolution of RVH

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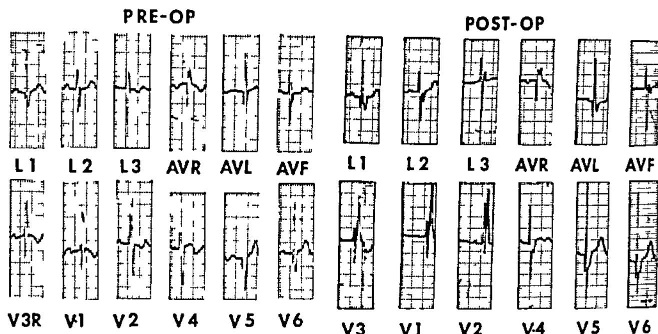


Fig 5 Further elevation and rightward orientation of the ÂQRS resulted as a consequence of a surgically induced RBBB

There was no significant change in the ÂQRS in those patients who had a resolution of isolated LVH or the absence of ventricular hypertrophy pre and postoperatively

VCG Preoperative VCG's were available in 16 patients The mean frontal plane QRS vector corresponded very closely to the AQRS of the ECG and a similar correlation was obtained with respect to ventricular hypertrophy A correlation could not be found, however, between the time at which the loop became superior and the presence of ventricular hypertrophy

Seven of the 16 patients had both pre and postoperative VCG's In all of these patients, except one with surgically induced RBBB, the mean QRS vector became less superior in the postoperative period with the resolution of the pre existing RVH or BVH (Fig 6) In addition there was an increase in the time at which the loop became superior in four and no change in three More importantly, the percentage of time which the loop spent superiorly decreased in all except the patient with surgically induced RBBB In this patient, the surgical induction of RBBB not only shifted the mean QRS vector to a more rightward and superior orientation but also increased the total percentage of time the vector spent superiorly The time at which the loop became superior did not change (Fig 7)

The mean follow up interval since surgery in the 29 patients was 4 4 years Of these four patients have complete RBBB in addition to a superior AQRS They have been followed for from 1 to 4 5 years The follow up period of all 29 patients has not been complicated with either ECG or clinical evidence of arrhythmias or the development of atrioventricular block

Discussion

Controversy over the mechanism of the superior ÂQRS in defects involving the endocardial cushions has existed for a number of years [1 2 13 21] Recently, several authors have suggested that the superior ÂQRS in these malformations is indicative of a left anterior hemiblock [1 3 22]

The results of the present study indicate that the preceding conclusion may not be true The presence of abnormal hemodynamics RVH, BVH, and RBBB, has a profound influence upon the degree of superiorness of the AQRS This study has shown that the ÂQRS markedly diminishes with the surgical correction of abnormal hemodynamics and the subsequent resolution of RVH or BVH With the persistence of ventricular hypertrophy postoperatively or the surgical induction of RBBB, the AQRS either remains unchanged or, in the latter instance becomes more superior and rightward The diminution of the ÂQRS in the postoperative OPSD also has been reported by others [24 25]

The dependency of the superior ÂQRS in

FRONTAL PLANE

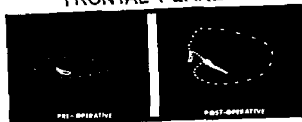


HORIZONTAL PLANE



Fig 6 The VCG corresponding to the patient in Fig 4 demonstrated the mean QRS vector in the frontal plane to decline following the resolution of RVH postoperatively

FRONTAL PLANE



HORIZONTAL PLANE



Fig 7 The VCG corresponding to the patient in Fig 5 showed the mean QRS vector to become more superior and rightward following a surgically induced RBBB

OPSD on various factors suggests that it is not due to a left anterior hemiblock but may be the result of a morphological abnormality in the conducting system To support this alternative explanation the available morphological and physiological studies were reviewed

The morphology of the conduction system in defects involving the endocardial cushions has been well illustrated by several authors [1 27] Lev demonstrated that the A V node is displaced posteriorly the bundle of His lies behind the lower margin of the defect and the left bundle branch (LBB) has a very short posterior radiation Feldt DuShane and Titus [9 2] further described the morphological features of the A V conduction system in not only A V canal defects but also in VSD and tetralogy of Fallot with superior mean QRS axis In addition to the findings of Lev these authors reported that the LBB is abnormally displaced posteriorly and has a relatively early origin from the common bundle Also the anterior radiations of the LBB were fewer in number than in normal hearts Early division of the posterior radiation of the LBB with small branches to the posterobasal portion of the left ventricle in OPSD was also demonstrated by Verduyn Lunel [27]

These anatomical findings have been confirmed by physiological studies using the technique of epicardial mapping Durrer Roos and Van Dam[1] found that in OPSD the posterobasal portion of the left ventricle was activated 30 msec earlier than in normal individuals Recently Boineau Moore and Patterson[28] demonstrated similar findings with epicardial mapping techniques in four patients and one dog with OPSD and a superior AQRS

In the dog Purkinje potential recordings showed a marked asynchrony in activation of the left ventricular endocardium with early posterior and delayed anterior depolarization This was in contrast to the almost synchronous activation of both anterior and posterior endocardial surfaces in a normal dog A detailed morphological study of the conduction system in the dog with the OPSD demonstrated posterior inferior displacement of the left ventricular Purkinje network with the posterior division of the LBB being markedly shorter than the anterior division Thus they concluded that the superior ÂQRS resulted from the marked asynchrony of left ventricular Purkinje activation secondary to a developmental asymmetry of the conduction system This evidence suggests that a morphological abnormality in the size and distribution of the LV conduction system alone can give rise to a superiorly oriented QRS axis

Based on the findings of this study as well as

the anatomical and physiological investigations reviewed, we propose the following hypothesis for the mechanism of the superior ÂQRS in OPSD Early activation of the posterobasal region of the left ventricle through congenitally asymmetric radiations of the LBB results in a variably marginal superior ÂQRS When a large left to right shunt elevated right ventricular pressure, RBBB, RVH, or BVH are superimposed, the resultant ÂQRS will be shifted more superiorly and to the right Correction of the altered hemodynamics and the subsequent resolution of chamber hypertrophy in the postoperative period shift the ÂQRS toward normal In contrast, persistence of the chamber hypertrophy or surgically induced RBBB maintains the ÂQRS oriented superiorly and to the right

A superior frontal plane ÂQRS is a consequence of asynchronous depolarization of the left ventricle with early activation of the posterobasal region of the heart This may be the result of a block in the anterior division of the LBB or a congenitally shortened posterior LBB division Up to now only a block of the anterior LBB division has been emphasized as the mechanism of a superior AQRS[1,3,7,8] In the present study, we propose that the combination of a malpositioned asymmetric left ventricular conduction system, with concurrent abnormal right sided hemodynamics RBBB RVH or BVH is responsible for the superior AQRS in OPSD

It is important to distinguish the mechanism of the superior ÂQRS in patients with associated surgically induced RBBB An interruption of the anterior fascicle of the LBB and RBBB would constitute a bifascicular block[29,30] It represents an entirely different clinical entity in contrast to a superior ÂQRS resulting from a congenitally malpositioned and asymmetric LV conduction system with surgically induced RBBB The difference is exemplified by their natural history While patients with true bifascicular block develop arrhythmias and progressive A V block[3,29,30] those with complete RBBB and a superior AQRS in postoperative OPSD remain asymptomatic This distinction is important in the clinical management and follow up of these patients

Summary

The influence of abnormal hemodynamics, ventricular hypertrophy, and right bundle branch block on the AQRS was studied pre and post operatively in 29 patients with OPSD The AQRS markedly diminishes with the surgical correction of abnormal hemodynamics and the subsequent resolution of RVH or BVH With the persistence of ventricular hypertrophy postoperatively or the surgical induction of RBBB, the ÂQRS either remains unchanged or, in the latter instance becomes more superior and rightward The dependence of the superior ÂQRS on these factors suggests that a left anterior hemiblock is not responsible for this ÂQRS In OPSD early activation of the posterobasal region of the left ventricle through an abnormally short posterior fascicle results in a minimal superior ÂQRS which is then exaggerated in the presence of abnormal hemodynamics, ventricular hypertrophy, or RBBB Thus the superior ÂQRS in OPSD with associated RBBB does not represent a true bifascicular block and has a different natural history and clinical significance

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Effects of tachycardia on the adequacy of subendocardial oxygen delivery in experimental aortic stenosis

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Subendocardial ischemia and infarction occur in association with aortic stenosis despite the absence of anatomic obstruction to coronary blood flow[1-3] This ischemia occurs when myocardial oxygen demands are increased as a result of the tachycardia of exercise or catecholamine infusion in patients with aortic stenosis[5-8] while similar increments in heart rate or stress do not cause electrocardiographic abnormalities in patients without left ventricular outflow obstruction or coronary artery disease[9-11] These observations suggest that the ischemia occurs because subendocardial oxygen delivery does not rise sufficiently to meet myocardial oxygen demands

Tachycardia shortens diastole more than systole and would tend to jeopardize blood flow to the subendocardium since this region receives its blood supply during this phase of the cardiac cycle Normally coronary flow is augmented by vasodilation during tachycardia to supply added oxygen to meet the rate induced rise in metabolic needs[9,11,13] In aortic stenosis the coronary arteries may be nearly maximally dilated under resting conditions so that coronary flow can meet the increased oxygen requirements of left ventricular systolic hypertension[6] Diastole which is shortened because of prolonged systolic ejection across the outflow obstruction even at slow heart rates, is reduced further with tachycardia Increasing heart rate in aortic stenosis may therefore limit available subendocardial blood supply and cause ischemia

We studied the interaction of tachycardia and aortic stenosis on the adequacy and distribution of subendocardial oxygen delivery in anesthetized dogs and assessed if indices derived from readily obtained measurements of blood pressure and oxygen content were useful in predicting subendocardial ischemia[14]

Methods

Eighteen mongrel dogs weighing 15 to 25 kilograms were anesthetized with 3 mg per kilogram of morphine intramuscularly and 15 mg per kilogram of chloralose administered intravenously A positive pressure respirator was used to provide ventilation with room air through an endotracheal tube After bilateral thoracotomy, polyethylene catheters were placed into the right atrium left atrium left ventricle, femoral artery and the ascending aorta just above the aortic valve Pressures were measured with Statham P23DB pressure transducers and recorded on a Hewlett Packard multichannel recorder The sino atrial node was crushed and heart rate controlled with a Grass physiologic stimulator Electrodes were sutured onto the surface of the left ventricle to record epicardial electrocardiograms and a unipolar platinum tip electrode was placed into the cavity of the left ventricle to record intracavitary electrocardiograms Change of the ST segment more than 2 mm above or below the isoelectric point was considered abnormal An umbilical tape tourniquet was placed around the ascending aorta for use in producing supravalvular aortic stenosis

Total and regional coronary flow was measured

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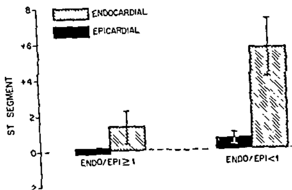


Fig 1 The change in the ST-segment (from isoelectric) with the normally even flow distribution across the left ventricular free wall (Endo/Epi ≥ 1) and with relative subendocardial underperfusion (Endo/Epi < 1) Note no significant changes occurred in the epicardial electrocardiogram despite marked elevation of the ST segment on the intracavitary electrocardiogram

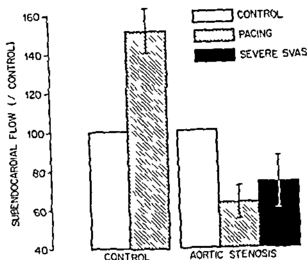


Fig 3 Change in subendocardial flow (from control values) with pacing of the normal heart pacing with aortic stenosis, and with severe aortic stenosis

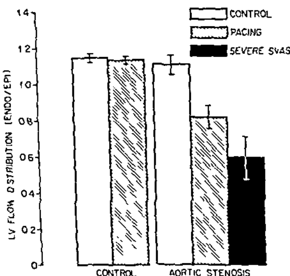


Fig 2 The changes in left ventricular flow distribution with aortic stenosis and pacing Note (1) No significant change in flow distribution when heart rate is increased in normal hearts without aortic stenosis or with moderate aortic stenosis at slow heart rates. (2) Relative subendocardial underperfusion (Endo/Epi < 1) with tachycardia and moderate aortic stenosis and with severe aortic stensis.

by determining the myocardial distribution of 8 to 10 micron microspheres labeled with [1] [1]Se [5]Sr and Sc injected into the left atrium A reference sample was collected from the femoral artery After completion of the experiment the dog was killed with $MgSO_4$ and the left ventricular free wall was divided into subendocardial subepicardial, and midmyocardial layers of approximately equal thickness These tissue samples were counted with a Nuclear Chicago pulse height analyzer and total and regional coronary flow calculated as described previously [15 16]

pH was measured by the Astrup method and arterial and venous oxygen contents measured directly with the Lex O Con Analyzer (Lexington Instrument Corporation)

Potential subendocardial blood flow was estimated from the diastolic pressure time index (DPTI) [7] obtained by planimetry of the area between the superimposed aortic and left ventricular pressure curves in diastole and potential subendocardial oxygen supply estimated from the expression $DPTI \times O_2$ content [4] Myocardial oxygen demands were estimated from the tension time index (TTI) [18] measured by planimetry of the area beneath the left ventricular pressure curve from the onset of ventricular systole to the dicrotic notch on the aortic pressure tracing The expression

$$\frac{DPTI \times O_2 \text{ content}}{TTI}$$

was used to estimate the supply/demand ratio of the left ventricular subendocardium [14]

Experimental procedure In control experiments heart rate was increased from 120 to 180 beats per minute in dogs without aortic stenosis Microsphere injections were made at both rates

At a heart rate of 120 beats per minute we produced aortic stenosis by tightening the snare around the ascending aorta until the supply/demand ratio ($DPTI \times O_2$ content/TTI) was reduced to between 15 and 20 and injected

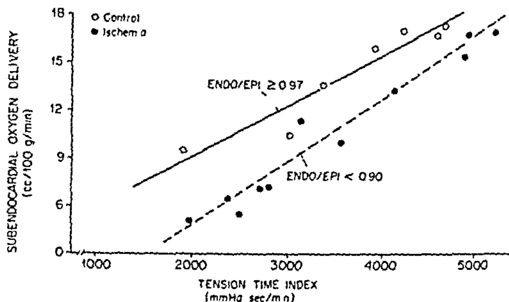


Fig 4 Left ventricular subendocardial oxygen delivery (subendocardial flow × oxygen content) is plotted against the TTI The solid line represents the regression line for animals with normal flow distribution (Endo/Epi ≥ 0 97) Y = 0 00319X + 2 74 R = 0 95 The broken line represents the regression line for animals with inhomogeneous flow distributions (Endo/Epi < 0.90) Y = 0 0044X − 4 76 R = 0 92 Note the significant reduction in oxygen delivery per unit of TTI when Endo/Epi < 0 90 Values for oxygen delivery per unit TTI fell between these regression lines when the Endo/Epi ratio was between 0 90 and 0 97 and were therefore excluded

microspheres In eight experiments, we increased the heart rate progressively (fixed level of aortic stenosis) and injected microspheres at that heart rate when the intracavitary electrocardiogram became abnormal (> 2 mm ST elevation) In four additional experiments where increasing heart rate did not cause changes in the intracavitary electrocardiogram we increased the level of aortic stenosis until endocardial electrocardiogram changes occurred and injected microspheres

Results

Correlation of electrocardiogram and coronary flow distribution In dogs without aortic stenosis left ventricular intracavitary and epicardial electrocardiograms were isoelectric at both slow and rapid heart rates (120 and 180 beats per minute), and coronary flow was evenly distributed across the left ventricular wall (endocardial/epicardial flow ratio 1 14 and 1 13 respectively)

With aortic stenosis at slow heart rates intracavitary and epicardial electrocardiograms were isoelectric and the parity of flow across the myocardium was maintained (endocardial/epicardial flow ratio 1 10) In the eight experiments with aortic stenosis where pacing produced a significant elevation of the ST segment on the intracavitary electrocardiogram (5 6 ± 2 0 mm S E) (Fig 1) coronary flow became redistributed away from the subendocardium and the endocardial/epicardial flow ratio was reduced to 0 81 ($p < 0.01$) (Fig 2)

In the four experiments where aortic stenosis was increased until significant ST elevation was seen on the intracavitary electrocardiogram endocardial/epicardial flow ratio was reduced to 0 59 (Fig 2) ($p < 0.01$)

Subendocardial oxygen delivery Arterial oxygen content did not change significantly during any experiment so that changes in oxygen delivery were determined principally by alterations to subendocardial blood flow Subendocardial flow increased an average of 51 per cent and remained homogeneously distributed when heart rate was increased from 120 to 180 beats per minute ($p < 0.01$) in control experiments In contrast left ventricular subendocardial flow fell 35 per cent ($p < 0.01$) when heart rate was increased in dogs with a fixed level of aortic stenosis (Fig 3)

The slope of the line describing subendocardial oxygen delivery relative to myocardial oxygen demands (estimated from the TTI) (Fig 4) was positive in all experiments There were, however significant differences in the oxygen delivery per unit of demand (TTI) when dogs with normal intracavitary electrocardiograms and homogeneous flow distributions were compared to those with electrocardiographic signs of ischemia and relative subendocardial underperfusion The

Table I

	Heart rate (beats/min)	O content (vol %)	DPTI (mm Hg sec)/min	TTI (mm Hg sec)/min	LV_{se} (cc/100 G/min)	Endo/Epi	Supply/Demand
Control							
M	1‿0	19 1	3 960	2 070	92	1 14	36 4
S D		3 3	600	314	21	0 07	4 6
S E		1 1	200	105	6 6	0 0[illegible]	1 5
N	9						
Pacing							
M	180	19 1	3 633	2 ‿66	139	1 13	27 0
S D		3 3	594	261	3[illegible]	0 07	3 9
S E		1 1	198	87	11	0 01	1 3
N	9						
SVAS							
M	131	20 7	3 430	3 586	190	1 10	17.8
S D	26	2 6	877	815	44	0 15	3 0
S E	7	0 8	2 7	257	14	05	0 9
N	10						
SVAS + Pacing							
M	154	20 6	1,596	3 124	6"	0 81	11 2
S D	"4	2 9	391	875	19	0 18	1 9
S E	8 5	1 0	138	309	10	0 06	0 7
N	8						
Severe SVAS							
M	136	21 0	1 227	4 686	75	0 59	5 5
S D	2?	1 1	214	148	18	0.22	1 1
S E	11	0 6	107	"4	6	0 11	0.5
N	4						

DPTI = diastolic pressure time index TTI = tension time index Endo/Epi = subendocardial to subepicardial flow ratio supply/demand = DPTI × O content/TTI M = mean S D = standard deviation S E = standard error N = number experiments LV_{se} = left ventricular subendocardial flow

highest values for subendocardial oxygen delivery at any level of demand were observed in dogs whose coronary flow remained evenly distributed across the myocardium and who had normal endocardial and epicardial electrocardiograms

Conversely subendocardial oxygen delivery for any level of demand (TTI) was lowest in dogs with redistribution of flow away from the subendocardium and abnormal electrocardiograms (elevated ST segments) ($p < 0.001$)

Changes in hemodynamic indices (Table I) In control studies, diastole occupied 69 per cent of the cardiac cycle when heart rate was 120 beats per minute and was shortened to 62 per cent of the cardiac cycle ($p < 0.01$) with tachycardia (180 beats per minute) (Fig 5 *A*)

With aortic stenosis the systolic ejection period of the left ventricle was prolonged at slow heart rates the diastolic filling period of the coronary arteries as therefore reduced 16 per cent below control values ($p < 0.01$) Tachycardia produced a more significant reduction in the duration of diastole than in control experiments so that diastole occupied only 50 per cent of the cardiac cycle in paced dogs with aortic stenosis (Fig 5 *B*) The greatest reduction in diastole (38 per cent of the cardiac cycle) was seen when the level of aortic stenosis was increased

Mean aortic diastolic blood pressure was 81 mm Hg during the control period in dogs without aortic stenosis and did not change significantly with tachycardia DPTI however fell from 3 960 mm Hg sec/min to 3 633 mm Hg sec/min (Table I) because diastole was shortened by tachycardia In contrast, although aortic diastolic blood pressure was *not* reduced with aortic stenosis the shortened diastole with slow rates reduced DPTI to 3 430 mm Hg sec/min ($p < 0.001$) With tachycardia diastolic pressure fell and the diastolic filling period of the coronary arteries was shortened further DPTI fell to 1 596 mm Hg sec/min ($p < 0.01$) (Fig 5 *B*) DPTI was also significantly reduced ($p < 0.01$) in the four experiments when aortic stenosis was made more

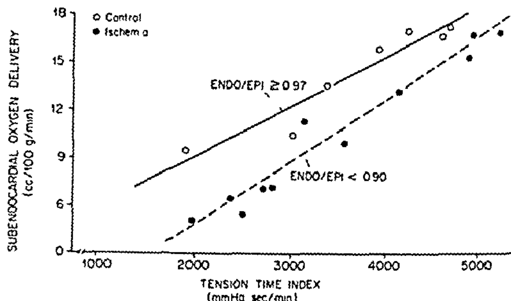


Fig 4 Left ventricular subendocardial oxygen delivery (subendocardial flow × oxygen content) is plotted against the TTI The solid line represents the regression line for animals with normal flow distribution (Endo/Epi ≥ 0.97) $Y = 0.00319X + 2.74$ $R = 0.95$ The broken line represents the regression line for animals with inhomogeneous flow distributions (Endo/Epi < 0.90) $Y = 0.0044X - 4.76$ $R = 0.92$ Note the significant reduction in oxygen delivery per unit of TTI when Endo/Epi < 0.90 Values for oxygen delivery per unit TTI fell between these regression lines when the Endo/Epi ratio was between 0.90 and 0.97 and were therefore excluded

microspheres In eight experiments, we increased the heart rate progressively (fixed level of aortic stenosis) and injected microspheres at that heart rate when the intracavitary electrocardiogram became abnormal (> 2 mm ST elevation) In four additional experiments where increasing heart rate did not cause changes in the intracavitary electrocardiogram, we increased the level of aortic stenosis until endocardial electrocardiogram changes occurred and injected microspheres

Results

Correlation of electrocardiogram and coronary flow distribution In dogs without aortic stenosis, left ventricular intracavitary and epicardial electrocardiograms were isoelectric at both slow and rapid heart rates (120 and 180 beats per minute), and coronary flow was evenly distributed across the left ventricular wall (endocardial/epicardial flow ratio 1.14 and 1.13, respectively)

With aortic stenosis at slow heart rates intracavitary and epicardial electrocardiograms were isoelectric and the parity of flow across the myocardium was maintained (endocardial/epicardial flow ratio 1.10) In the eight experiments with aortic stenosis where pacing produced a significant elevation of the ST segment on the intracavitary electrocardiogram (5.6 ± 2.0 mm S E) (Fig 1) coronary flow became redistributed away from the subendocardium and the endocardial/epicardial flow ratio was reduced to 0.81 ($p < 0.01$) (Fig 2)

In the four experiments where aortic stenosis was increased until significant ST elevation was seen on the intracavitary electrocardiogram endocardial/epicardial flow ratio was reduced to 0.59 (Fig 2) ($p < 0.01$)

Subendocardial oxygen delivery Arterial oxygen content did not change significantly during any experiment so that changes in oxygen delivery were determined principally by alterations to subendocardial blood flow Subendocardial flow increased an average of 51 per cent and remained homogeneously distributed when heart rate was increased from 120 to 180 beats per minute ($p < 0.01$) in control experiments In contrast left ventricular subendocardial flow fell 35 per cent ($p < 0.01$) when heart rate was increased in dogs with a fixed level of aortic stenosis (Fig 3)

The slope of the line describing subendocardial oxygen delivery relative to myocardial oxygen demands (estimated from the TTI) (Fig 4) was positive in all experiments There were however significant differences in the oxygen delivery per unit of demand (TTI) when dogs with normal intracavitary electrocardiograms and homogeneous flow distributions were compared to those with electrocardiographic signs of ischemia and relative subendocardial underperfusion The

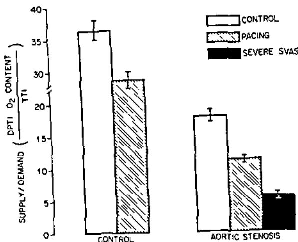


Fig 6 The supply/demand ratio (DPTI × O content/TTI) in normal hearts (no aortic stenosis) before and after tachycardia (pacing) and in hearts with varying levels of aortic stenosis and heart rate Note the progressive fall in the supply/demand ratio with each intervention

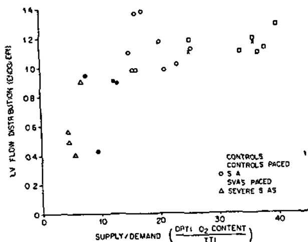


Fig 7 Coronary flow distribution across the left ventricular (LV) free wall (endocardial to epicardial Endo/Epi) on the ordinate is plotted against the supply/demand ratio (DPTI × O content/TTI) on the abscissa Note flow remains homogeneously distributed across the myocardium (Endo/Epi > 1 0) over a wide range of supply to demand ratios (15 to 40) Subendocardial underperfusion (Endo/Epi < 1 0) occurs only when this supply to demand ratio falls below a critical value

severe TTI increased 132 per cent above control values ($p < 0\,01$)

In control experiments without aortic stenosis the supply/demand ratio (DPTI O_2 content/TTI) fell from 36 to 27 with tachycardia ($p < 0\,01$) (Fig 6) In contrast the supply/demand ratio was reduced more significantly (18 $p < 0\,01$) during control conditions in dogs with aortic stenosis With pacing this ratio was reduced further to 11 2 in the eight dogs whose intracavitary electrocardiograms showed significant ST elevation Tachycardia did not change this ratio in four dogs whose intracavitary electrocardiograms remained isoelectric Increasing the level of aortic stenosis reduced the supply/demand ratio to 5 5 and resulted in ST elevation of the intracavitary electrocardiogram

Correlation of changes in flow distribution with supply/demand ratio In control experiments coronary flow remained evenly distributed across the myocardium despite a wide range of supply/demand ratios at slow heart rates and a significant reduction of this ratio with pacing ($p < 0\,01$) (Fig 7) Although the supply/demand ratio was reduced at slow heart rates with aortic stenosis left ventricular subendocardial and subepicardial muscle received approximately equivalent flows whenever this ratio exceeded 15 Conversely reduction of the supply/demand ratio to below 15 by either increasing heart rate with a fixed level of aortic stenosis or increasing the level of aortic stenosis resulted in a decrease of the proportion of total left ventricular flow delivered to the subendocardium (Fig 7) These lower supply/demand ratios and changes in flow distribution were always associated with a significant elevation of the ST segment on the intracavitary electrocardiogram

Discussion

The present studies confirm the clinical and experimental observations of others[8, 9, 20] that coronary flow increases in response to tachycardia in normal hearts This suggests that the coronary arterioles dilate to insure sufficient oxygen supply to meet the rate induced rise in metabolic demands of all layers of the normal heart Although tachycardia shortens the diastolic filling period of the coronary arteries (when most subendocardial perfusion occurs) the normally homogeneous distribution of left ventricular flow is maintained with increasing heart rate and no electrocardiographic evidence of ischemia occurs[13, 21]

In contrast tachycardia caused relative subendocardial underperfusion and electrocardiographic changes of ischemia in dogs with experimental aortic stenosis We produced aortic stenosis by constricting the aorta above rather than at the

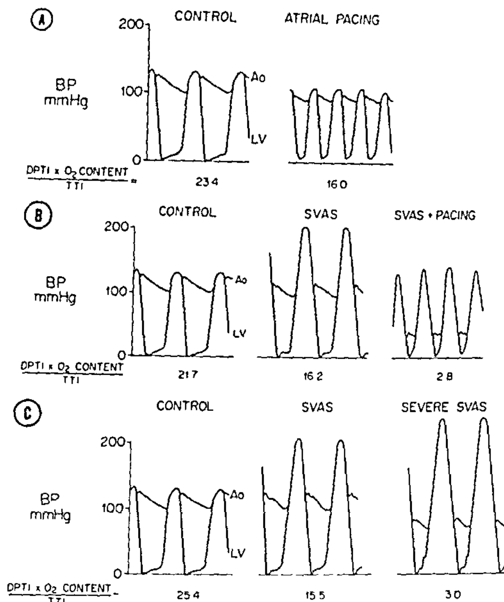


Fig 5 Simultaneous recordings of aortic and left ventricular pressures The stippled area represents the DPTI The TTI is the area under the ventricular pressure curve from the onset of ventricular systole to the dicrotic notch *A* effect of atrial pacing in control hearts *B* effect of pacing hearts with moderate supravalvular aortic stenosis (SVAS) *C* effect of increasing the severity of supravalvular aortic stenosis Note the marked decrease in both systolic and diastolic blood pressures when tachycardia is superimposed upon aortic stenosis

severe aortic diastolic pressure fell and the diastolic filling period of the coronary arteries was shortened significantly by prolonged ventricular emptying (Fig 5 *C*)

Left ventricular end diastolic pressure decreased with pacing in all control experiments In contrast increasing heart rate with aortic stenosis caused a rise in left ventricular end diastolic pressure in three dogs and resulted in no significant change in the others The highest values for left ventricular diastolic pressure occurred when the level of aortic stenosis was increased (Fig 5 *C*)

In control experiments the resting aortic systolic pressure was 101 mm Hg and TTI 2 020 mm Hg sec /min With tachycardia, aortic systolic pressure rose slightly and the duration of systole per minute increased oxygen demands as estimated by the TTI increased 27 per cent

As a result of the systolic hypertension imposed by ventricular outflow obstruction peak left ventricular pressure was 166 mm Hg at slow heart rates, TTI increased 77 per cent above control values ($p < 0.01$) Aortic pressure could not, however, be sustained when heart rate was increased with aortic stenosis Despite the significant reduction (25 per cent) in aortic pressure TTI fell only slightly as the duration of systole was further prolonged by tachycardia Peak left ventricular pressure rose to 210 mm Hg and the duration of systole prolonged to 62 per cent of the cardiac cycle when aortic stenosis was made more

demand (product of blood pressure and heart rate) than did normal patients Two patients developed angina and a raised left atrial pressure following heavy exercise indicating the inadequacy of myocardial oxygen delivery and resultant ventricular failure In our studies three dogs with aortic stenosis increased left ventricular end diastolic pressure following tachycardia

The determinants of subendocardial oxygen supply and demand are accounted for by the ratio DPTI × O_2 content/TTI Our previous studies have shown that through coronary autoregulation flow remains evenly distributed across the left ventricular myocardium over a range of supply/demand ratios (from 35 to 10) [4] We made use of these observations in designing the present experiment the snare around the ascending aorta was tightened until the supply/demand ratio was lowered to between 15 and 20 This resulted in a gradient across the stenotic segment ranging from 30 to 100 mm Hg coronary flow remained evenly distributed across the myocardium

Although the supply/demand ratio fell in normal hearts with induced tachycardia it remained within the normal range the even distribution of flow across the left ventricular myocardium was preserved In contrast pacing dogs with fixed levels or aortic stenosis caused a more pronounced reduction of the supply/demand ratio and resulted in a redistribution of flow away from the subendocardium and electrocardiographic evidence of ischemia In these experiments subendocardial ischemia occurred at higher supply/demand ratios (< 15) than in our previous studies This may be related to the underestimation of oxygen demand by the TTI when the inotropic state of the heart is increased by tachycardia We also observed ischemia at higher supply/demand ratios in our previous studies with isoproterenol

In the four dogs with aortic stenosis in whom tachycardia failed to lower the supply/demand ratio the intracavitary electrocardiogram remained normal In these experiments we produced ischemia by increasing the level of aortic stenosis We conclude from these observations that (1) ischemia results when flow/TTI (supply/demand) is reduced below a critical level (2) flow will be adequate despite a fall in this ratio as long as the coronary bed can dilate to meet increased demands or decreased perfusion pressure (3) once the coronary bed is fully dilated flow becomes dependent on hemodynamic factors (estimated by DPTI) and ischemia (inadequate flow/TTI) can be predicted from DPTI/TTI and (4) this ratio is dependent on the interaction of heart rate and aortic stenosis rather than the absolute heart rate or aortic gradient This conclusion is consistent with the recent report of Lewis and associates [5]

The present studies were performed with normal levels of hemoglobin and arterial oxygen content We expect that lesser degrees of aortic stenosis or smaller increments in heart rate will result in myocardial ischemia if arterial oxygen content is reduced (i e anemia hypoxia) [1, 33]

Summary

We studied the interaction of tachycardia and aortic stenosis on the adequacy of subendocardial oxygen delivery In 18 open chest dogs with acute supravalvular aortic stenosis we produced subendocardial ischemia by increasing either heart rate (atrial pacing) or the severity of aortic stenosis Ischemia was determined from ST elevation of the intracavitary electrocardiogram Subendocardial oxygen supply was assessed by measuring subendocardial flow (radioactive microspheres 8 to 10 microns) and arterial oxygen content and related to simultaneous oxygen demand [estimated from the tension time index (TTI)] The adequacy of the supply/demand relationship in the subendocardium was estimated from the ratio DPTI × O_2 content (supply)/TTI (demand)

Subendocardial ischemia occurred at aortic gradients ranging from 30 to 100 mm Hg and heart rates from 120 to 180 beats per minute Ischemic hearts were characterized by (1) redistribution of coronary flow away from the subendocardium (endo/epi flow ratio < 1.0) (2) reduced subendocardial oxygen delivery per unit of demand (TTI) ($p < 0.01$) (3) failure to lower left ventricular end diastolic pressure with tachycardia and (4) supply/demand ratios (DPTI × O content/TTI) below 15 ($p < 0.01$)

These findings suggest that (1) the principal determinant of subendocardial ischemia in aortic stenosis is the unfavorable alteration of the supply/demand relationship caused by the interaction between heart rate and severity of stenosis rather than absolute heart rate or aortic gradient and (2) the adequacy of subendocardial oxygen

aortic valve The mechanism of ischemia is, however, comparable to that of valvular aortic stenosis i e, inadequate oxygen delivery relative to demand [2] Although coronary systolic pressure and flow are increased with supravalvular aortic stenosis, the determinants of subendocardial flow which is diastolic are compromised severely

Ischemia, which occurred whenever coronary flow became redistributed away from the subendocardium was observed at different heart rates and levels of aortic stenosis Our previous experiments showed histochemical signs of ischemia when the proportion of total coronary flow delivered to the subendocardium became reduced [23] It is our hypothesis that this ischemia occurs when subendocardial oxygen delivery cannot increase sufficiently to meet simultaneous oxygen demands and that determination of this supply/demand imbalance can be predicted from readily obtained indices

Subendocardial oxygen delivery is determined by coronary flow and arterial oxygen content The subendocardium is more vulnerable to ischemia than other parts of the heart because it must receive most or all of its blood supply during diastole (systolic compressive forces impede flow to the subendocardium during myocardial contraction) [24] Since the heart normally extracts almost all of its delivered oxygen,[25] coronary blood flow must increase to provide added oxygen if requirements rise (i e tachycardia) [9, 1, 26]

The adequacy of subendocardial blood supply may be maintained initially by coronary autoregulation but once maximum vasodilation occurs, subendocardial flow is determined by the diastolic coronary driving pressure and duration These determinants of subendocardial perfusion are expressed by the diastolic pressure time index (DPTI) Our previous studies have shown that this index estimates potential subendocardial blood supply[17] and that subendocardial oxygen delivery can be estimated from the expression DPTI × O_2 content [11]

In the present experiments tachycardia produced a small reduction of DPTI in normal hearts as the diastolic filling period of the coronary arteries was shortened Coronary flow however, increased despite a decreased DPTI indicating that coronary vasodilation occurred

With aortic stenosis, DPTI was reduced significantly even at slow heart rates as systolic ejection across left ventricular outflow tract obstruction was prolonged Tachycardia shortened diastole further, and to a greater extent than it did in normal hearts Since diastolic blood pressure also fell as heart rate rose, DPTI was reduced strikingly by increasing the heart rate with aortic stenosis In contrast to the findings in normal hearts subendocardial flow fell with increasing heart rate in dogs with aortic stenosis These observations suggest that the coronary arteries were already dilated maximally and that the reduction in the coronary driving pressure and duration of diastole (DPTI) with tachycardia accounted for the observed relative underperfusion of the subendocardium

The failure of left ventricular end diastolic pressure to fall (as it did in normal hearts) following tachycardia in aortic stenosis (left ventricular end diastolic pressure rose in three dogs) suggests that myocardial function was impaired rather than enhanced by pacing

The adequacy of subendocardial flow can be assessed only by comparing it to some estimate of oxygen requirements Resting oxygen requirements are high with aortic stenosis because the ventricle must perform increased pressure work and the duration of systole is prolonged [2, 4] Tachycardia increases oxygen demands as the myocardium develops tension more frequently each minute In these experiments we used the TTI to estimate myocardial oxygen demands since this readily obtained value has been shown to correlate well with changes of oxygen consumption in compensated hearts [11, 27] Boerth and co workers [9] have shown that tachycardia may exert an inotropic effect since oxygen consumption per beat increases with heart rate This may explain why we observed a 51 per cent increase in coronary flow in normal hearts while TTI only increased 30 per cent with tachycardia

We found that oxygen delivery to the subendocardium per unit of demand (TTI) was significantly reduced in dogs with ischemic electrocardiograms and altered transmural flow distributions (Fig 4) We interpret the ischemic intracavitary electrocardiogram to provide evidence that subendocardial oxygen delivery was inadequate [9, 30, 31] This conclusion is supported by the studies of Holmberg and Varnauskas[9] who found that patients with coronary artery disease had less coronary flow increment relative to

External counterpulsation for cardiogenic shock following cardiopulmonary bypass surgery

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The persistent failure to wean a patient from cardiopulmonary bypass after open heart surgery is an ominous development which until recently implied a hopeless prognosis This outlook is currently being tempered with new hope by reports of the successful use of intra aortic balloon counterpulsation as a means of temporary cardiocirculatory assist in this situation [1]

An alternative and noninvasive method of counterpulsation is now available which produces counterpulsation by applying phasic pressures to the lower extremities in synchronism with the cardiac cycle This technique for producing diastolic augmentation was introduced by Clauss and co workers and subsequently developed by Clauss Dennis and associates [8] and others in response to the inherent difficulties and risks associated with invasive methods Within the past 2 years it has found increasing clinical application [1 11] This method can be rapidly and easily employed in the operating room to assist the patient being weaned from bypass and for several hours or days thereafter Being non invasive it provides the physiologic benefits of counterpulsation and can be conducted much longer than intra aortic balloon counterpulsation while requiring a minimum of technical assistance

Past use of the device has been almost exclusively limited to the application of positive pressure to the legs during diastole This mode has been shown to produce good diastolic augmentation improved coronary filling and blood flow and increased cardiac output but has been somewhat less effective than the intra aortic balloon in reducing left ventricular afterload and end diastolic pressure [8 3]

With the recent addition of a negative pressure phase e g application of pressure less than ambient to the limbs during systole increased counterpulsation including a further reduction in both preload and afterload is achieved (see Fig 1) [13]

In this communication we report on four patients who after undergoing open heart surgery lapsed into cardiogenic shock when cardiopulmonary bypass was discontinued and could not be supported by the usual pharmacologic means In each case the low cardiac output state responded well to external peripheral counterpulsation and the cardiocirculatory status stabilized during the period of temporary assistance all patients survived and were discharged

Case reports

Case 1 A 60 year old man had progressed to a functional class IV status (N Y H A) with advanced valvular heart disease and chronic atrial fibrillation prior to initial cardiologic evaluation Heart catheterization confirmed severe aortic and mitral insufficiency and produced these hemodynamic data left ventricular pressure 150/35 mm Hg aortic pressure 150/50 mm Hg pulmonary artery pressure 83/37 mm Hg with mean capillary wedge pressure 35 mm Hg right ventricular pressure 83/18 mm Hg Cardiac output was severely reduced (2 0 L/min) and cardiac index was 0 94 L/min /M Selective coronary arteriograms revealed no obstructive disease

During the operation after aortic and mitral valve replacement systolic blood pressure fell to levels of 50 to 60 mm Hg with each attempt to discontinue cardiopulmonary bypass despite care to monitor volume loading and despite administration of inotropic (Isuprel and calcium) and vasopressor (epinephrine) agents With each attempt to slowly withdraw bypass support central venous pressure (CVP) rose to 40 cm H O and pulmonary artery end-diastolic pressure (monitored

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Cardiassist External pressure circulatory assist a product of Medical Innovations, Inc Waltham Mass. 0 154

delivery can be assessed from readily obtained measurements of blood pressure and oxygen content

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Cardia ist E tern l pressu e cir ulatory assist a p oduct of Medical In at ns, I Waltham Mass 02154

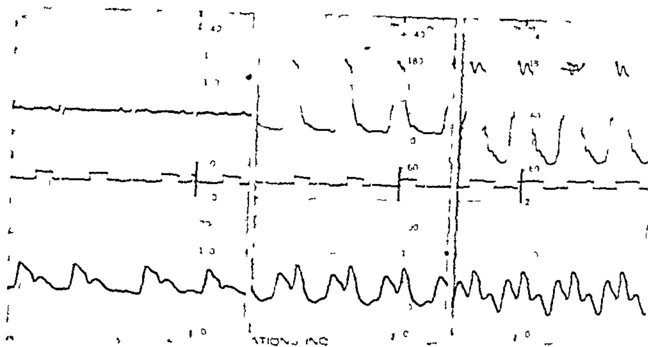


Fig 1 Example of counterpulsation produced by Cardiassist external pressure circulatory assist in a patient with chronic stable angina (courtesy of the New England Medical Center Hospitals) *Left panel* Control recordings of ECG (*top*) and brachial artery pressure (*bottom*) employing positive pressure only *Right panel* Recordings of applied pressure to legs (*top*) and brachial artery pressure (*bottom*) with Cardiassist operating with alternating positive and negative pressure

in lieu of left heart pressures) rose to 35 to 40 mm Hg as the systemic pressure fell

After repeated unsuccessful attempts to wean the patient from cardiopulmonary bypass support by our usual procedure the peripheral external counterpulsation device used in the coronary care unit of the hospital was brought to the operating room The sterile drapes were raised from the foot of the operating room table to the level of the patient s pelvis with care being taken not to contaminate the operative field The patient s legs were raised and the external pressure encasement of the Cardiassist device was positioned on the lower half of the operating room table The legs were then lowered into the pressure encasement and secured for application of external counterpulsation compression The Cardiassist controlling console was positioned at the foot of the table The lower extremities and Cardiassist unit were then redraped and the over patient surgical instrument stands were repositioned over the unit and the lower half of the operating room table in their usual position This was accomplished without interruption of attention to the operative procedure within the patient s chest or to extracorporeal circulation (the ascending aortic was the site of arterial cannulation)

External counterpulsation produced an immediate augmentation of diastolic pressure of 20 to 25 mm Hg Phasic 1 1 external compression of the lower extremities was triggered by temporary cardiac pacing at the rate of 85 per minute to overdrive a much slower rate of ventricular response with atrial fibrillation Mean systemic arterial pressure rose from less than 50 mm Hg to over 75 mm Hg within a few minutes Pulmonary artery end-diastolic pressure fell more slowly to 20 mm Hg and CVP to 24 to 26 cm H_2O After over an hour of anuria a diuresis developed within 20 minutes of counterpulsation Cardiopulmonary bypass support could be totally discontinued within 15 minutes and all vasopressors were stopped within 20 minutes of the start of counterpulsation

The patient was supported by the external Cardiassist in the operating room for 2¼ hours during which time heparin effects were neutralized the chest wound was closed and the cardiovascular and metabolic status was observed to stabilize Cardiassist support was briefly interrupted while the patient and the apparatus were transported from the operating room to the surgical intensive care unit During this brief interruption the peak systolic pressure fell to levels of 70 to 80 mm Hg and pulmonary artery end-diastolic pressure rose to the previous levels but again these responded immediately when external counterpulsation was resumed After 22 hours of counterpulsation support during which brief trial periods without the device indicated the continued need for this support it was possible to gradually discontinue counterpulsation The cardiocirculatory status of the patient thereafter remained stable cardiac compensation was maintained and the patient subsequently fully recovered and was discharged home on the fifteenth postoperative day

Case 2 A 59 year old man developed a large ventricular aneurysm subsequent to a massive myocardial infarction Symptoms of progressive heart failure developed and the patient s condition deteriorated gradually to a functional class IV (N Y H A) within 10 months Cardiac catheterization in addition to demonstrating a large aneurysm and its paradoxical motion during cardiac systole revealed complete obstruction of the proximal left anterior descending coronary artery at its origin and no significant obstruction in the other major coronary artery branches Left ventricular end diastolic pressure was elevated at rest (30 mm Hg) and rose to 38 mm Hg after these contrast studies Right ventricular (64/4 mm Hg) and pulmonary arterial (60/20 mm Hg) pressures were elevated Cardiac output was reduced (3 0 L /min) and the cardiac index was 2 1 L /min /M^2

After left ventricular aneurysmectomy in which the apex and a large part of the anterior and lateral para apical left

ventricular free wall were excised (64 sq cm) the patient could not be weaned from cardiopulmonary bypass Our usual practice in this situation—i.e first gaining th Frank Starling effect by very carefully monitoring left heart pressures while volume loading by gradually returning volume from the reservoir of the oxygenator to the patient and then slowly withdrawing bypass support while infusing vasopressors and stimulating the heart with inotropic agents—failed also to prevent the state of cardiogenic shock that promptly devel oped when bypass support was withdrawn

While cardiopulmonary bypass support was maintained the patient s lower extremities were placed in the Cardiassist d vice Good augmentation of diastolic aortic pressure was produced immediately A temporary pacemaker set at the rate of 85 beats per minute to override sinus bradycardia was used to trigger the device Mean systemi blood pressure rose 20 mm Hg to levels over 75 mm Hg within a few minutes pulmonary artery end-diastolic fell slowly from levels of 35 to 38 mm Hg to 20 to 24 mm Hg and cardiopulmonary bypass was successfully discontinued Within 20 to 30 minutes all infusions of pressor and inotropic agents were discontinued and operation was normally concluded With continuous support of the peripheral counterpulsation the patient s cardiovascular status stabilized and Cardiassist was discon tinued 4½ hours after operation The patient recovered and was subsequently discharged on the eleventh postoperative day Improvement has continued and the patient is now 10 months after an urysmectomy functionally class II

Case 3 A 69 year old man had had progressive symptoms of congestive heart failure since age 40 due to rheumati aortic and mitral valve disease At the time he underwent heart catheterization and operation his condition was functionally class IV Catheterization studies confirmed biventricular heart failure left ventricular dilatation associated with severe aortic regurgitation combined with moderately severe mitral stenosis and mild mitral regurgitation The tricuspid valve was competent Atrial fibrillation with multifocal ventricular ectopy was present The following pressure data were re corded left ventricle 168/34 mm Hg aorta 190/70 mm Hg pulmonary artery 70/35 mm Hg with mean capillary wedge pressure of 35 mm Hg and V wave of 50 mm Hg right ventricular pressure 70/10 mm Hg Cardiac output was reduced (3 4 L/min) and the cardiac index was 1 96 L /min / M

At operation after successful replacement of the aortic and mitral valves the patient could not be weaned from cardiopul monary bypass Meticulous attention had been paid to our techniques to protect the myocardium during valve replace ment i.e deep hypothermic perfusion (25 C) surface cooling and continuous perfusion of both coronary arteries without electrical fibrillation of the heart The usual pharma cologic measures with infusions of potent vasopressors and inotropic agents after carefully monitored volume loading to achieve optimal effects of the Frank-Starling principle were not effective Cardiopulmonary bypass was resumed after a brief interruption to rapidly transfer the arterial cannula to the ascending aorta The femoral arteriotomy was then repaired and the groin wound was dressed open The lower extremities were then placed in the Cardiassist device and external peripheral counterpulsation was started Because of complete heart block, a temporary pacemaker was again used and served to trigger the counterpulsation While external counterpulsation continued a mean systemic blood pressure of 75 mm Hg was readily maintained. Vasopressors and inotropic drugs were discontinued and cardiopulmonary bypass support was ultimately discontinued after 40 minutes of counterpulsation The patient s cardiovascular status stabilized and Cardiassist support was discontinued after 7½ hours The patient s postoperative recovery was slow compli cated by pulmonary atelectasis and a mild pump lung syndrome Five days of assisted ventilation and subsequent oxygen and intensive pulmonary therapy were required However cardiac compensation was maintained This patient is symptomatically improved but he is functionally restricted and his status is only class III at 12 months after operation

Case 4 A 45-year-old woman had long had symptoms of slowly progressive heart failure due to calcific congenital aortic stenosis Consideration of definitive surgical treatment of the progressing cardiac disease had first been deferred six years previously because a coincidental discovery of mam mary carcinoma required radical mastectomy and postop erative radiation therapy Operation was again postponed when, 3½ years later a contralateral mammary carcinoma required radi al mastectomy and engendered a guarded immediate prognostic outlook However accelerated deterio ration in her cardiac status from class III to class IV within a 5-month period prompted cardiologic reevaluation and the following hemodynamic data were recorded at heart catheter ization peak systolic gradient across the aortic valve 84 mm Hg left ventricular end diastolic pressure 31 mm Hg cardiac output 3 1 L/min and cardiac index 2 1 L /min /M

At operation after replacement of the aortic valve cardio genic shock gradually developed with each attempt to discon tinue cardiopulmonary bypass Intraoperative peripheral external counterpulsation was employed and after a contin uous 6-hour period of Cardiassist support all vasopressors could be discontinued and the patient s cardiovascular status stabilized After several trial periods off the apparatus it was possible to totally discontinue support after 13½ hours Although the patient s cardiovascular status was improved her recovery was further complicated She was ultimately discharged with a residual partial right hemiparesis and after treatment of an upper gastrointestinal hemorrhage due to a gastric ulcer that had necessitated discontinuation of antico agulation therapy The patient subsequently succumbed to a cardiac arrhythmia 4½ months after operation

Discussion

External pressure circulatory assist employs compression of the lower extremities during dias tole to produce diastolic augmentation at the aortic root which enhances coronary perfusion Postoperatively in the patient with low cardiac output this effect may be of critical importance in supporting subendocardial muscle which is particularly vulnerable to ischemia since it receives most of its blood supply during dias tole [14]

The removal of leg compression (or the applica tion of negative pressure) during systole coupled with the enhanced arterial run off produced by diastolic augmentation tends to reduce cardiac work by effectively decreasing aortic impedance

left ventricular preload, and tension time index. In addition, external peripheral compression increases cardiac output by its effect on the venous circulation—an increase in the pressure gradient for venous return during diastole which augments right atrial filling and hence cardiac output.

The above mentioned effects (increased coronary perfusion and cardiac output and the reduction of cardiac work) combine to increase cardiac efficiency and promote a better balance between myocardial oxygen supply and demand.

For reasons not yet well understood, cardiopulmonary bypass reduces myocardial efficiency, at least transiently. The measure of support this method is capable of providing to the post-cardiotomy patient over a period of minutes or hours may not be the cure all in every case, but clearly does have a potential to afford both improved cardiac physiology and the time for the recovery of depressed myocardial function. Wherever sufficient myocardial function is recoverable and necessary circulatory support is provided, the device will prove to be life saving in some marginal patients.

Recently, Buckberg and associates[14] have clarified the role of coronary blood flow and its role in oxygen supply to the myocardium as it relates to fatal post cardiotomy myocardial failure and subendocardial necrosis. Whereas these workers emphasize that the duration of diastole and the mean diastolic pressure in the aorta largely determine coronary blood flow and oxygen supply to the heart, others have also reported that unphysiologic coronary perfusion,[15] prolonged treatment with norepinephrine,[16] Isuprel,[17] and electrically maintained fibrillation[18] contribute to subendocardial ischemia and the development of post cardiotomy myocardial failure. Hypertrophied hearts appear to be predisposed to such injury. When myocardial failure and ischemic injury are manifest by depressed left ventricular function and a low cardiac output state results, physiologic considerations suggest not only that an improved coronary blood flow is required to bring myocardial oxygen supply and demand into better balance, but also that early application of counterpulsation will contribute to this effort to recover depressed heart function by reduction of cardiac work while increasing cardiac output. On the contrary, current pharmacologic treatment which emphasizes prolonged infusions of potent catecholamines and inotropic agents can become deleterious and unphysiologic in its effects.[14-17] In our limited experience which we report, it has been our observation that the successful intraoperative application of counterpulsation has permitted immediate reduction and early discontinuation of infusions of these pharmacologic agents in all cases. When these pharmacologic agents alone are clearly ineffective, the early intraoperative application of counterpulsation in this group of patients would appear to be a more physiologic therapy, or to even offer a potentially more effective combined treatment of the patient who cannot be weaned from cardiopulmonary bypass by pharmacologic means alone.

Albeit limited, our experience has been dramatic and attests to the value of the intraoperative use of this noninvasive external method of cardiocirculatory assist. Our surgical house staff, recognizing that these patients would surely otherwise have succumbed, have dubbed the device the "miracle worker."

The inconsistent results of counterpulsation when applied to cardiogenic shock patients in coronary care units have been attributed to its delayed application after inception of shock and to the fact that the patients treated do not constitute a homogeneous group. Such patients represent a complex variety of cardiocirculatory dysfunctions grouped together only because the presenting situation is their low cardiac output state. Patients who fail to come off cardiopulmonary bypass after a corrective operation do not necessarily represent a specific pattern of dysfunction but do constitute a more homogeneous and possibly more tractable group and one that can be treated almost from the inception of the shock state. For these reasons, the most favorable results may be expected in this group of surgical patients even though they require the counterpulsation support even before cardiopulmonary bypass can be discontinued, or quite soon thereafter. Of all presently available cardiac assist devices, aortic balloon counterpulsation and external peripheral counterpulsation are the only two that are reported to improve the survival rate of patients with cardiogenic shock and that appear to be sufficiently safe to justify widespread clinical use at this time. Moreover, the obvious advantages and simplicity of the noninvasive external counterpulsation method which we report may make easy this application

of counterpulsation in a group of patients for whom the outlook has heretofore been so poor

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Table 1 Left ventricular catheterization and angiographic data

	Age (yr)	HR (beats/min.)	LVSP (mm. Hg)	LVEDP (mm. Hg)	SAP (mm Hg)	DAP (mm. Hg)	CI (L/min./M)	Max dP/dt (mm. Hg/sec)	Vpm (ML/sec)	h (cm)	EDVI (ml./M)	LMMI (gm./M)
Group 1 controls (n = 9)												
Mean	27 6	78	113	10 4	113	72	3 9	1 640	1 41	0 76	99	89
±1 S D	±7 6	±14	±13	±3 0	±13	±9	±0 9	±300	±0 20	±0 15	±24	±24
Group 2 pressure load (n = 10)												
Mean	41 7	68	207	24 8	118	69	3 1	1 710	1 05	1 47	136	241
±1 S D	±12 0	±11	±20	±7.5	±17	±10	±0 5	±430	±0 26	±0 19	±33	±41
P (group 2 vs. group 1)	NS	NS	<0 001	<0 001	NS	<0 05	<0 05	NS	<0 01	<0 001	<0 02	<0 001
Group 3 volume load (n = 9)												
Mean	36 6	82	141	20 3	128	60	3 8	1 465	1 07	1.26	212	254
±1 S D	±11 6	±13	±14	±7 7	±13	±14	±0 7	±420	±0 33	±0 19	±44	±42
P (group 3 vs. group 1)	NS	NS	<0 001	<0 01	<0 05	NS	NS	NS	<0 02	<0 001	<0 001	<0 001
P (group 3 vs group 2)	NS	<0 05	<0 001	NS	NS	NS	<0 05	NS	NS	<0 05	<0 001	NS

Abbreviations used in Tabl 1. HR = *heart rate* LVSP = *left ventricular systolic pressure.* LVEDP = left ventricular end-diastolic pressure. SAP = systolic aortic pressure. DAP = diastolic aortic pressure CI = cardiac ind x. *max dP/dt* = maximal rate of left ventricular pressure rise V_{pm} = peak measured velocity of shortening of the contractile elements during iso *olumetric contraction* h = wall thickness. EDVI = end-diastolic volume *per* square meter of body surf ce area (BSA). LMMI = *left ventricular muscle mass per square meter of BSA.* P = probability (unpaired t test) NS = not significant (P > 0 05). S D = standard deviation.

the procedure After right heart catheterization a Statham SF_1 tipmanometer was introduced into the left ventricle either by the retrograde route through an atrial septal defect or following punc ture of the septum The pressure in the ascending aorta was measured by a Statham P23Db pressure transducer connected to a red Oedman catheter or by a second SF tipmanom eter Mean aortic valve gradients were deter mined by integration of the area between the left ventricular and aortic pressure tracings during the ejection phase of left ventricular contraction The magnitude of valvular incompetence was estimated by the thermodilution technique Cardiac output was determined by the Fick prin ciple in most cases in addition by the thermodi lution method The following measurements were made from pressure tracings recorded on an Elec tronics for Medicine DR/8 or DR/16 *oscillograph* at a paper speed of 200 mm per second (Fig 1) *left* ventricular systolic pressure (LVSP) left ventricular end-diastolic pressure (LVEDP) sys tolic aortic pressure (SAP) diastolic aortic pres sure (DAP) From the left ventricular high fidelity pressure tracing the first derivative (dP/dt) was obtained by a circuit with a time constant of 0 8 msec [1] The quotient of dP/dt and ventric ular pressure (P) i e (dP/dt)/P was determined instantaneously throughout the cardiac cycle by an analog calculating unit with a time constant of 1 1 msec [3] The velocity of the *contractile* elements during the isovolumic phase of left ventricular contraction (V_{CE}) was calculated as [(dP/dt)/K P] in terms of muscle lengths (ML) per second [10 2 2] K represents the modulus of elasticity of the series elastic components and amounts to 28 cm [2] Contractility was assessed by the actual value of peak measured velocity of shortening (V_{pm}) [23] Left ventricular cineangio grams were performed in the right anterior oblique and in the anteroposterior position Contrast dye* was delivered in amounts of 25 to

* Urografin 76%, Schering Berlin West Germany

Contractility of the hypertrophied human left ventricle in chronic pressure and volume overload

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Several studies in animals[1-5] and man[6-10] suggest that left ventricular hypertrophy is associated with a decrease in contractility At the present time the decrease in contractility is considered to contribute to the clinical deterioration of the patient with heart failure On the other hand it has been speculated[11] that the reduction in contractility is compensatory in that it prolongs life by easing the burden on the chronically overloaded heart Apart from this teleological speculation the question is not settled whether the type of stimulus to hypertrophy plays a role as to what extent myocardial contractility is reduced in left ventricular hypertrophy

A large body of data obtained from animal[1-4] and clinical[7-10] studies indicates that left ventricular hypertrophy due to pressure load is accompanied by a decrease of contractility Whether hypertrophy consequent to chronic volume load leads per se to an impairment of the contractile state remains a matter of controversy No alteration of contractile function was observed in isolated papillary muscles[12] from cats exposed to a prolonged volume load and in the chronically volume overloaded left ventricle of the dog[13,14] One study showed even an enhanced ventricular performance under volume load[15] In man various results have been reported[16-18]

The present study was designed to contribute to the question whether myocardial hypertrophy from chronic volume load (VL) is associated with decreased contractility as found in hypertrophy due to chronic pressure load (PL) The comparison of contractility was carried out in two groups of patients with VL and PL in which the extent of myocardial hypertrophy as estimated from the angiographically determined left ventricular muscle mass was similar

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Material and methods

A total of 28 patients were studied The *first* group (controls) comprised nine patients with normal left ventricular function and the following diagnoses five atrial septal defects in two of which partial anomalous pulmonary venous drainage was present (left to right shunt 42 to 82 per cent of pulmonary flow), one right sided aortic arch one pectus excavatum two functional murmurs The *second* group with left ventricular PL was composed of 10 patients with severe aortic stenosis (mean systolic pressure gradients ranging from 56 to 90 mm Hg) Some patients showed additional mild to moderate aortic incompetence (regurgitation fraction 0 11 to 0 48) and/or trivial mitral regurgitation (regurgitation fraction 0 05 to 0 08) The *third* group with left ventricular VL comprised 9 patients with moderate to severe aortic incompetence (regurgitation fraction ranging from 0 48 to 0 70) Three of them had mild aortic stenosis (mean systolic pressure gradients between 19 and 33 mm Hg) Two of them had in addition to the aortic regurgitation a mitral incompetence with regurgitation fractions of 0 50 and 0 53 respectively The mean age was not significantly different in the three groups (see Table I) All patients showed sinus rhythm QRS did not exceed 0 1 sec in duration

The patients were premedicated by 10 mg of chlordiazepoxide* given orally one hour prior to

* Librium Hofmann La Roche Basel Switzerland

ciated with an impaired inotropic state Proposed mechanisms for the decrease of contractility are altered calcium binding in the sarcoplasmatic reticulum or increased nonphosphorylating respiration of the mitochondria [4,5] The situation is less clear as far as the influence of chronic volume overload is concerned Neither in the papillary muscle [2] nor in the intact *left ventricle*[1,4] *was a* decreased contractility consequent to volume overload observed One study reports even an enhanced performance of the canine left ventricle under volume load [15] In man there is controversy aortic regurgitation of similar degree may or may not lead to depressed left ventricular function [6] The comparison of the effects of the two types of load on myocardial contractility was attempted recently by Mason and co workers [17,8] Their results suggest that contractility is depressed under both pressure and volume load whereby the impairment of contractile state was more marked in volume than in pressure load The two groups of patients were however not matched with respect to left ventricular mass or to another parameter indicative of the extent of left ventricular hypertrophy

The purpose of our study was to compare the effects of pressure and volume load on the contractile state of the left ventricle in man As index of myocardial contractility we have chosen the peak measured velocity of shortening of the contractile elements during the isovolumic phase of left ventricular contraction We felt justified in doing so because it has been shown that the maximal extrapolated velocity of the contractile elements (Vmax) is closely related to V_{pm} in patients with different pre and afterload due to chronic heart disease In contrast to Vmax however V_{pm} is a finite value without the difficulties of extrapolation particularly encountered in aortic valve disease The situation in mitral or aortic incompetence deserves an explanation because in both conditions there is no isovolumic phase of left ventricular contraction In mitral incompetence dP/dt is likely to be depressed because blood escapes into the left atrium before the opening of the aortic valve V_{CE} is underestimated progressively in the course of this part of left ventricular *contraction* V_{pm} *however* occurs very early after the onset of contraction and is probably only moderately affected by fiber shortening prior to aortic valve opening [2] In aortic incompetence diastolic regurgitation stretches the left ventricle until the pressure in the left ventricle exceeds diastolic aortic pressure Since ventricular filling is a determinant of the rate of left ventricular pressure rise[29] aortic regurgitation is expected to cause values of dP/dt and V_{CE} larger than those that would have existed without additional filling during early contraction The quantitative effect of this phenomenon is presumably small because the pressure gradient between aorta and left ventricle and hence the regurgitant flow are small when contraction starts and decrease rapidly toward the moment of pressure crossover

In the group with PL as well as in the group with VL V_{pm} was significantly depressed as compared to the control group But there was no *significant difference of* V_{pm} *in the two pathologic* groups This finding is at variance with the results of studies in the papillary muscle[12] and in the intact canine left ventricle [13,5] A possible explanation for this discrepancy is the different duration of the volume overload in the reported animal studies volume load was imposed on the left ventricle for approximately 50 days whereas in clinical heart disease it lasts for many years It could well be that in addition to the increase in left ventricular mass other structural changes of the myocardium consequent to chronic volume overload which take a longer time to develop are involved in altering contractility It has been suggested that the decrease of contractility in chronic volume load is accentuated by slippage of myofibrils which occurs later than the development of myocardial hypertrophy due to pressure load [18]

Summary

Nine patients with normal left ventricles (C) 10 patients with pressure load (PL) due to predominant aortic stenosis and 9 patients with predominant volume load (VL) due to aortic incompetence were studied by left ventricular high fidelity pressure measurements and cineangiography Peak measured velocity of the contractile elements (V_{pm}) used as index of contractility and left ventricular muscle mass (LMMI) were determined The patients with PL and VL were matched with respect to LMMI In PL LMMI was 241 ± 41 and in VL 254 ± 42 gm per square meter Both were sizably increased ($P < 0.001$) as compared to LMMI in C (89 ± 24 gm per square meter) V_{pm} was 1.41 ± 0.20 ML per second in C In PL and VL V_{pm} was reduced to 1.05 ± 0.26 ($P < 0.01$) and to 1.07 ± 0.33 ML per

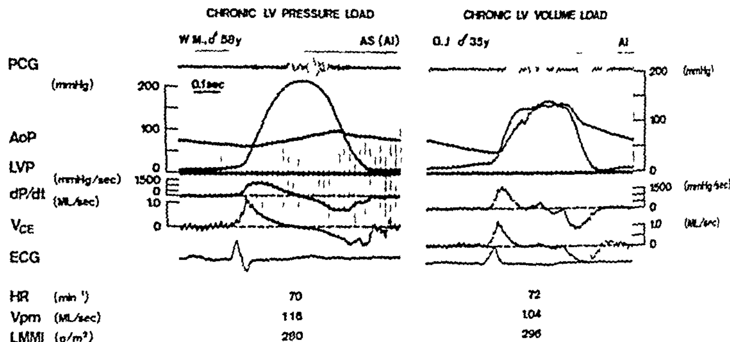


Fig 1 Recordings from a patient with aortic stenosis (pressure load mean systolic pressure gradient 90 mm Hg aortic valve area 0 4 cm²) and from a patient with aortic insufficiency (volume load regurgitation fraction 0 58) At a similarly increased left ventricular muscle mass (*LMMI*) peak measured velocity of shortening of the contractile elements (*Vpm*) is reduced to comparable values *PCG* = phonocardiogram *AoP* = aortic pressure *LVP* = left ventricular pressure *dP/dt* = first derivative of LVP V_{CE} = velocity of shortening of the contractile elements *ECG* = electrocardiogram (Lead II) *HR* = heart rate Both *LVP* and *AoP* were measured by tipmanometers.

40 ml by a ECG triggered power injector* Volume measurements were made by the single-plane method of Greene and associates[20] End diastolic wall thickness was estimated from the anteroposterior cineangiograms according to the technique of Rackley and co workers[21] The difference between total left ventricular volume and end diastolic volume times the specific gravity of myocardium (1 05 gm per milliliter) equals the left ventricular muscle mass

Results

The findings are summarized in Table I Left ventricular systolic pressure was significantly higher in the group with PL (207 ± 20 mm Hg) as compared with the control group (113 ± 13 mm Hg) In the group with VL LVSP was also moderately increased (141 ± 14 mm Hg) LVEDP was similar in the two pathologic groups and significantly higher than in Group 1 SAP was slightly but significantly higher in Group 3 than in the control group, DAP was somewhat higher in the control group as compared to the two pathologic groups Wall thickness was larger in the diseased left ventricles than in the normals The left ventricles with PL showed the highest figure for wall thickness which was significantly higher than in the group with VL The left ventricular muscle mass per square meter (LMMI) was similar in the groups with PL and VL, it was nearly three times higher than in the normal group The end diastolic left ventricular volume per square meter (EDVI) was 99 ± 24 ml per square meter in the control group In Group 2 EDVI was only slightly increased (136 ± 33 ml per square meter, $P < 0.02$) In Group 3 the augmentation of EDVI was much more pronounced (212 ± 44 ml per square meter, $P < 0.001$) Cardiac index and heart rate showed only minor differences in the three groups V_{pm} was 1 41 ± 0 20 muscle lengths (ML) per second in the control group In PL as well as in VL V_{pm} was reduced to 1 05 ± 0 26 ($P < 0.01$) and to 1 07 ± 0 33 ML per second ($P < 0.02$) V_{pm} in Group 2 was not significantly different from V_{pm} in Group 3

Discussion

In recent years several experimental[1-3] and clinical[6-10] studies have been carried out to investigate the influence of chronic pressure overload on myocardial contractility From these investigations it is apparent that myocardial hypertrophy consequent to pressure overload is asso

*Contrac Siemens, Zürich, Switzerland.

ciated with an impaired inotropic state Proposed mechanisms for the decrease of contractility are altered calcium binding in the sarcoplasmatic reticulum or increased nonphosphorylating respiration of the mitochondria [5] The situation is less clear as far as the influence of chronic volume overload is concerned Neither in the papillary muscle [2] nor in the intact left ventricle[13 14] was a decreased contractility consequent to volume overload observed One study reports even an enhanced performance of the canine left ventricle under volume load [15] In man there is controversy aortic regurgitation of similar degree may or may not lead to depressed left ventricular function The comparison of the effects of the two types of load on myocardial contractility was attempted recently by Mason and co workers [17 18] Their results suggest that contractility is depressed under both pressure and volume load whereby the impairment of contractile state was more marked in volume than in pressure load The two groups of patients were however not matched with respect to left ventricular mass or to another parameter indicative of the extent of left ventricular hypertrophy

The purpose of our study was to compare the effects of pressure and volume load on the contractile state of the left ventricle in man As index of myocardial contractility we have chosen the peak measured velocity of shortening of the contractile elements during the isovolumic phase of left ventricular contraction We felt justified in doing so because it has been shown that the maximal extrapolated velocity of the contractile elements (Vmax) is closely related to V_{pm} in patients with different pre and afterload due to chronic heart disease [4 5] In contrast to Vmax however V_{pm} is a finite value without the difficulties of extrapolation particularly encountered in aortic valve disease The situation in mitral or aortic incompetence deserves an explanation because in both conditions there is no isovolumic phase of left ventricular contraction In mitral incompetence dP/dt is likely to be depressed because blood escapes into the left atrium before the opening of the aortic valve V_{CE} is underestimated progressively in the course of this part of left ventricular contraction V_{pm} however occurs very early after the onset of contraction and is probably only moderately affected by fiber shortening prior to aortic valve opening [28] In aortic incompetence diastolic regurgitation stretches the left ventricle until the pressure in the left ventricle exceeds diastolic aortic pressure Since ventricular filling is a determinant of the rate of left ventricular pressure rise[29] aortic regurgitation is expected to cause values of dP/dt and V_{CE} larger than those that would have existed without additional filling during early contraction The quantitative effect of this phenomenon is presumably small because the pressure gradient between aorta and left ventricle and hence the regurgitant flow are small when contraction starts and decrease rapidly toward the moment of pressure crossover

In the group with PL as well as in the group with VL V_{pm} was significantly depressed as compared to the control group But there was no significant difference of V_{pm} in the two pathologic groups This finding is at variance with the results of studies in the papillary muscle[12] and in the intact canine left ventricle [13 15] A possible explanation for this discrepancy is the different duration of the volume overload in the reported animal studies volume load was imposed on the left ventricle for approximately 50 days whereas in clinical heart disease it lasts for many years It could well be that in addition to the increase in left ventricular mass other structural changes of the myocardium consequent to chronic volume overload which take a longer time to develop are involved in altering contractility It has been suggested that the decrease of contractility in chronic volume load is accentuated by slippage of myofibrils which occurs later than the development of myocardial hypertrophy due to pressure load [8]

Summary

Nine patients with normal left ventricles (C) 10 patients with pressure load (PL) due to predominant aortic stenosis and 9 patients with predominant volume load (VL) due to aortic incompetence were studied by left ventricular high fidelity pressure measurements and cineangiography Peak measured velocity of the contractile elements (V_{pm}) used as index of contractility and left ventricular muscle mass (LMMI) were determined The patients with PL and VL were matched with respect to LMMI In PL LMMI was 241 ± 41 and in VL 254 ± 42 gm per square meter Both were sizably increased ($P < 0.001$) as compared to LMMI in C (89 ± 24 gm per square meter) V_{pm} was 1 41 ± 0 20 ML per second in C In PL and VL V_{pm} was reduced to 1 05 ± 0 26 ($P < 0.01$) and to 1 07 ± 0 33 ML per

second ($P < 0.02$) V_{pm} in PL was not different from V_{pm} in VL Heart rate showed no major difference in the three groups It is concluded that in two groups of patients with predominant PL and VL matched with respect to LMMI left ventricular contractility was depressed to a similar extent regardless of the stimulus to hyper trophy

The authors acknowledge gratefully the secretarial work of Mrs Mehmel and Mrs Bonomo

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Case reports

Complex atrial arrhythmias studied by suction electrode technique

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Among old people with chronic cardiovascular and pulmonary disease complex atrial arrhythmias often appear[1 5] Multifocal atrial pacemakers or changed atrial focus in the presence of a depressed sinus node sometimes in the presence of aberrant atrial conduction and in the presence of atrioventricular conduction disturbances with junctional rhythms may be found in these situations

Probable important factors in the pathogenesis of these complex atrial arrhythmias are diffuse atrial disease (ischemia fibrosis and distention) and damage to the sinus node and atrioventricular conduction system [2 6]

Monophasic action potential (MAP) recorded from the right atrium using a suction electrode technique allows a magnification of the electrical atrial activity which can be better analyzed in this way and gives information about the refractoriness of the myocardium [1 14] We have used a bipolar electrode catheter made from polyethylene tubes with insulated wires inside introduced percutaneously without x ray control as a bedside procedure After locating the catheter in the right atrium under electrocardiographic monitoring the bore was gently pushed against the endocardium negative pressure was then applied and MAP could be recorded [1]

The recordings from the elderly patients with atrial arrhythmias are presented

Case reports

Case 1 D T a 69 year-old man with coronary heart disease and chronic pulmonary disease was admitted in congestive heart failure and treated with diuretics and digitalis.

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He was diagnosed as having a chaotic atrial mechanism on intracavitary electrogram (Fig 1) where more than three types of P waves could be seen with different P Q intervals, and in the sixth complex a hisian beat was observed with dissociation between atrial and ventricular activity In Fig 2 a simultaneous recording of right atrium monophasic action potential (RAMAP) intracavitary electrogram (IC) and Leads I and II of the standard electrocardiogram allows a better analysis of the atrial activity The P Q interval ranging in normal limits, is different from beat to beat The distance from the beginning of atrial depolarization and the onset of the RAMAP curve (P MAP) is also different from beat to beat This P MAP interval represents the distance from the origin of atrial ectopic activity to the place where the tip of the suction electrode is fixed and may also indicate the speed of the intra atrial conduction The fourth complex from the upper part and the third and seventh complexes from the lower strip are junctional beats with and without aberrant atrioventricular conduction atrial activity being blocked The RAMAP duration calculated on the isoelectric line is 470 msec the normal values being 310 msec

Case 2 F R a 79 year old man treated for congestive heart failure was diagnosed as having coronary heart disease and associated chronic pulmonary disease The electrocardiographi diagnosis was multiple multifocal atrial premature beats and first degree atrioventricular block In Figs 3 and 4 simultaneous recordings of RAMAP IC and a standard electrogram are presented The third complex in the figure is a blocked atrial premature beat the seventh and eighth beats are also atrial premature beats all from different foci The same phenomenon can be seen in Fig 4 where the third fifth and sixth complexes in the upper panel are premature beats arising from different foci The third complex in the bottom panel is a blocked premature beat the seventh complex is also a premature beat P Q and P MAP intervals are different during premature activity The RAMAP duration in this case is 400 msec more than normal values.

From time to time a focal atrial tachycardia was found in this patient as shown in Fig 5 where regular tachycardic atrial activity can be seen with blocked ventricular conduction which is activated by a junctional pacemaker in the first two complexes and in the following four complexes a 3/1 atrioventricular block takes place

Discussion

The patients presented are elderly men with coronary heart disease and chronic pulmonary

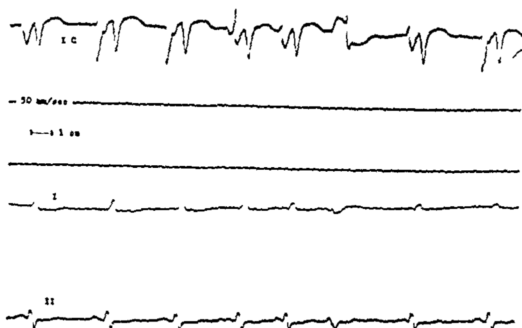


Fig 1 Simultaneous recordings in patient D T of intracavitary electrogram (IC) and Leads I and II of the standard electrocardiogram Paper speed is 50 mm per second For discussion see text.

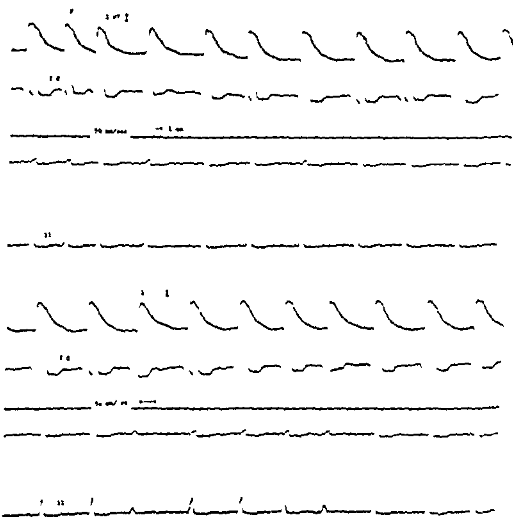


Fig 2 Simultaneous recordings in the same patient as in Fig 1 of right atrium monophasic action potential (RAMAP) intracavitary electrogram (IC) and Leads I and II with a paper speed of 50 mm per second Panels A and B are a continuous strip For discussion see text

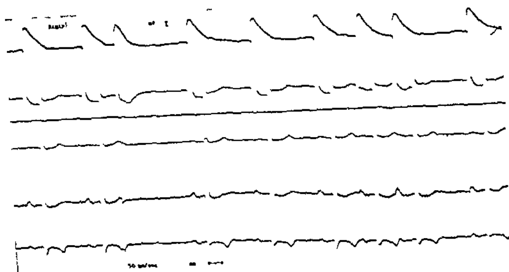


Fig 3 In patient F R. a simultaneous recording of the right atrium monophasic action potential (RAMAP) intracavitary electrogram (IC) and Leads I II and III Paper speed is 50 mm per second For discussion see text

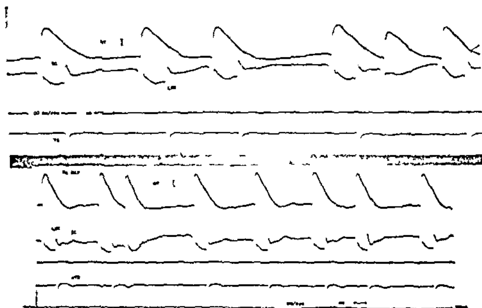


Fig 4 Right atrium monophasic action potential (RAMAP) intracavitary electrogram (IC) and Lead aV recorded simultaneously in the same patient as in Fig 3 In the upper panel the paper speed is 100 mm per second while in the bottom one the paper speed is 50 mm per second For discussion see text

disease who were in congestive heart failure This clinical situation together with diuretic and digitalis treatment may play a role in the pathophysiology of these complex atrial arrhythmias [2,5] Because of ventricular irregularity in both cases atrial fibrillation was suspected before an electrocardiographic examination was *performed* The multiple atrial foci were associated with intra atrial and atrioventricular disturbances and junctional activity

The long duration of RAMAP in these cases suggests an increased refractoriness of atrial muscle which could explain the stability of focal activity hindering the micro re entry and the disorganization of atrial activity specific for atrial fibrillation [2,1,3]

The recordings obtained from these two patients demonstrate the usefulness of the monophasic action *potential* technique in the analysis of atrial arrhythmias allowing a good amplifica

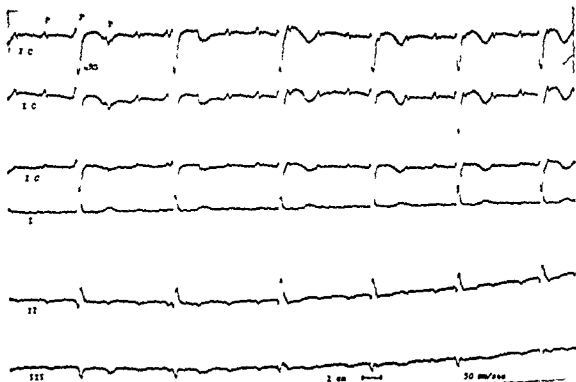


Fig 5 Simultaneous recording in the same patient as in Figs. 3 and 4 of three intracavitary electrograms (IC) and Leads I II and III of the standard electrocardiogram Paper speed is 50 mm per second For discussion see text.

tion of atrial activity and the estimation of myocardial refractoriness

Summary

Two elderly patients with coronary heart disease, chronic pulmonary disease, and complex atrial arrhythmias are presented The suction electrode technique for right atrium monophasic action potential recording was used This recording allows better analysis of the atrial arrhythmias and estimates the stability of focal activity

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The hemodynamic effects of supraventricular tachycardia in ventricular septal defect with pulmonary outflow tract obstruction

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The clinical association of rapid atrial tachycardia with increased cyanosis in a patient with tetralogy of Fallot has previously been reported A similar finding occurring in a child with a ventricular septal defect and pulmonary artery banding was recently documented at this institution The patient developed supraventricular tachycardia during cardiac catheterization allowing analysis of the hemodynamic mechanisms

Case report

P T a six year old female was admitted to Babies Hospital for elective cardiac catheterization A ventricular septal defect with hyperkinetic pulmonary hypertension was documented at two months of age The infant did not respond well to a maximal cardiotonic regimen and a pulmonary artery banding was successfully carried out one month later Her subsequent clinical course was excellent including normal growth and development Digoxin had been discontinued at two years of age The patient had never exhibited cyanosis either at rest or during exercise nor was she known to have had any cardiac dysrhythmias A second cardiac catheterization was scheduled in preparation for definitive surgical correction of the ventricular septal defect and "debanding of the pulmonary artery

Physical examination disclosed an acyanotic well-developed girl in no distress Positive physical findings were confined to the heart. A systolic thrill was palpable at the left base A Grade IV/VI long systolic ejection murmur was audible at the left base with radiation across the precordium S was normally split.

Cardiovascular study was performed the following day Following premedication with meperidine 50 mg promethazine 1^9 5 mg and chlorpromazine 12 5 mg cardiac catheterization was carried out percutaneously from the right femoral vein The catheter entered the superior vena cava right atrium, right ventricle pulmonary artery and the ascending aorta via the ventricular septal defect During the procedure with the catheter in the right atrium the patient suddenly developed supraventricular tachycardia accompanied by significant hemodynamic changes Oxygen saturations pressures and arterial blood gas determinations were obtained during the tachycardia and during sinus rhythm and in both 100 per cent oxygen and room air A right ventricular angiocardiogram was obtained during normal sinus rhythm Systemic and pulmonary blood flows were determined by the indirect Fick technique using assumed oxygen consumption data derived from the tables of LaFarge and Miettinen

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Results

The data is summarized in Table I A left to right shunt ($Qp/Qs = 1.5$) was documented under conditions of normal sinus rhythm Arterial samples were fully saturated ruling out a significant right to left shunt The right ventricular angiocardiogram showed this chamber to be hypertrophied The infundibular area narrowed during systole Bidirectional shunting occurred at the ventricular level

With the development of supraventricular tachycardia the dynamics shifted markedly with reversal of the ventricular shunt and the development of arterial desaturation There was no significant change in arterial pressure nor in right ventricular systolic and end diastolic pressures The total pulmonary artery right ventricular peak systolic gradient was also unaltered There was however the development of a right ventricular outflow tract gradient not previously encountered (Fig 1) A significant decrease in both pulmonary and systemic blood flows occurred though systemic blood flow now slightly exceeded pulmonary blood flow (right to left shunt)

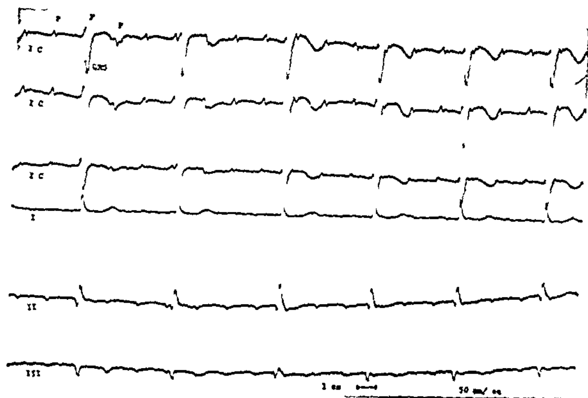


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Summary

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Table I Hemodynamic data (room air)

Rhythm (rate)	Per cent saturation	*Assum d oxygen consumption = 149 c c /min /M* — Flow data: Pulmonary AV difference (c c %)	Systolic AV difference (c c %)	Qp (l /m /M)	Qs (L/m./M2)	Per cent shunt	Pressure data: Ao	PA	RV body	SVR (RU/M)	Arterial blood gas s: Po (mm Hg)		Pco (mm Hg)	
											Rm Air	100% O	Rm Air	100% O
NSR (110)	97	4 3	6 4	3 5	2 3	34 L→R	87/57 m=70	15/8	83/4	30	80		33	
SVT (240)	68	13 4	7 8	1 1	1 9	42 R→L	90/50 m=62	12/6	82/4	29	34 o	42	32	32

AO = aorta NSR = n rmal sinus rhythm PA = pulmo ary artery Qs = systemic flow Qp = pulmonary flow RU = resistance units RV = right ventri le SVT = supra entricula tachycardia

tetralogy of Fallot therefore an increase in right ventricular outflow tract obstruction when heart rates are increased is not unexpected

In the patient described who essentially has the potential hemodynamics of tetralogy of Fallot the shunt initially left to right reversed during supraventricular tachycardia causing sig nificant cyanosis The constancy of the total right ventricle pulmonary artery gradient with a decrea ed pulmonary blood flow and the devel opment of a right ventricular outflow tract gradi ent indicates that the right ventricular outflow tract was the site of increased resistance the pulmonary artery band site being relatively fixed The potential right ventricular outflow tract obstruction was supported by the presence of a thickened contracting infundibulum on angio cardiography during normal sinus rhythm

The mechanism of anoxic spells in tetralogy of Fallot has more recently been attributed to a cycle generated by the onset of paroxysmal hy perpnea In the present case however hyper pnea cannot be implicated as the Pco remained constant Whereas paroxysmal hyperpnea may explain the spell in certain situations it is not the sole etiology and infundibular spasm as the causative agent cannot be discounted especially in the presence of tachycardia

This study documents by hemodynamic data a phenomenon previously noted clinically Should a patient with tetralogy of Fallot dy namics present with spells and supraventricular tachycardia the immediate course of action should be directed toward the elimination of the arrhythmia If the supraventricular tachycardia is not the etiology of the sudden hypoxic episode it most certainly contributes to its adverse ef fects

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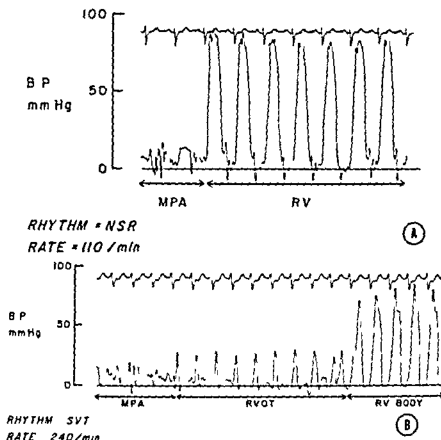


Fig 1 *A* Withdrawal tracing recorded across the pulmonary outflow tract during normal sinus rhythm Peak systolic gradient = 69 mm Hg *B* Withdrawal tracing during supraventricular tachycardia An area of infundibular obstruction is now seen Total peak systolic gradient = 70 mm Hg MPA main pulmonary artery RVOT right ventricular outflow tract RV right ventricle NSR normal sinus rhythm and SVT supraventricular tachycardia

whereas the reverse was true during normal sinus rhythm (left to right shunt) Systemic vascular resistance was not measurably different The Pco remained normal and the administration of 100 per cent oxygen did not affect the level of arterial desaturation

Discussion

Shunt dynamics through a large ventricular septal defect can best be explained by the relative levels of resistance to ejection of the two ventricles the pressures in the two chambers being equal The data indicate that the systemic vascular resistance was essentially unchanged under the varying conditions of the study A major change in resistance, therefore occurred at the site of the right ventricular outflow tract where a definite gradient appeared Although the pulmonary artery to right ventricle peak systolic gradient remained essentially identical (normal sinus rhythm 69 mm Hg, supraventricular tachycardia 70 mm Hg) the pulmonary flow during supraventricular tachycardia decreased by one third and right to left shunting occurred

These dynamics can be accounted for by an increase in the resistance to right ventricular outflow despite the equality of the gradients under the two conditions Had the resistance remained unchanged the gradient would have been expected to decrease with a decrease in total flow

In patients with tetralogy of Fallot, infundibular hypertrophy with spasm and increasing right ventricular outflow tract obstruction is thought to account for right to left shunting with ensuing hypoxic spells [2,5] Increased obstruction at the right ventricular outflow tract in such patients has been related to beta stimulation of the right ventricular myocardium, and has been relieved with propranolol [6,7] Patients with tetralogy of Fallot in whom supraventricular tachycardia has occurred have been noted to develop hypoxic spells and spells have been induced in such patients during rapid atrial pacing [1,8] Rapid heart rates are well known to increase myocardial contractility as well as decrease the volume of the right ventricle secondary to significant shortening of the diastolic filling phase [9,11] In a patient with

Ethambutol empirically a month after discharge Two weeks later he was readmitted with increasing weakness The vital signs were unchanged from the previous admission and he was still febrile (99 8° F) The chest x ray demonstrated cardiomegaly and left atrial enlargement and the ECG revealed atrial flutter with 2 1 A V block right axis deviation depressed S T segments from V_4 to V_6 and depressed T waves throughout The white cell count ranged from 10 000 to 15 000 per cubic millimeter and the hemoglobin was 8 8 Gm per 100 ml The alkaline phosphatase was 218 I U and the total protein was 5 6 Gm per 100 ml (albumin 2 3 Gm per 100 ml globulin 3 3 Gm per 100 ml) Protein electrophoresis demonstrated alpha globulin 1 2 Gm per 100 ml, beta globulin 0 7 Gm per 100 ml gamma$_1$ globulin 0 4 Gm per 100 ml , gamma$_2$ globulin 1 0 Gm per 100 ml

While in the hospital the patient developed palpable inguinal and axillary lymphadenopathy An exploratory laparotomy was performed and enlargement of the liver was noted but no lymphadenopathy was found A liver biopsy splenectomy and multiple lymph node biopsies were performed Following surgery he was awake and afebrile, however several hours later he suffered cardiac arrest

Following resuscitation his pupils remained fixed and dilated and he was without spontaneous respirations Frequent episodes of ventricular fibrillation were converted electrically Thirty six hours later it became impossible to sustain pulse and blood pressure and the patient died

Discussion

DR CHEITLIN To summarize the case this is a 52 year old man who for many years had as his only complaint prolonged episodes of atrial arrhythmias apparently paroxysmal atrial tachycardia which had been controlled by digitalis from 1963 to 1971 In 1971 he developed atrial flutter with variable A V block converted by cardioversion and controlled with quinidine In the summer of 1973 he began to have drenching night sweats fever malaise and loss of appetite The weight loss was marked—25 pounds in six weeks—the type one sees with hyperthyroidism chronic illness or most commonly malignancy Hyperthyroidism is less likely in this patient because of his decreased appetite His chest x ray at the onset of his present illness was within normal limits and his laboratory evaluation revealed a sterile pyuria unresponsive to antibiotics Physical examination at that time revealed no cardiac abnormality The patient had no murmurs no hypertension or enlargement of his heart and the first and second heart sounds were described as normal Absent from this history and in a way worrisome in its absence is the lack of shortness of breath orthopnea or paroxysmal nocturnal dyspnea because on the subsequent chest x rays it appears that he developed pulmonary venous hypertension the peculiar nature of which we will see when we look at the x rays in sequence

My understanding is that the hemoglobin or hematocrit dropped gradually over the period of his illness reminiscent of the anemia that is seen with a chronic illness or neoplasm with bone marrow depression There was no evidence presented which would suggest hemolysis A description of the erythrocyte morphology on the peripheral blood smear and haptoglobin and bilirubin values would have been helpful The possibility exists that the drop in hemoglobin was due to chronic or even acute blood loss A sudden drop in hemoglobin is not due to bone marrow depression it must be due either to hemorrhage or to hemolysis

Possible causes for the patient s fever were extensively evaluated with numerous blood and urine cultures yielding no growth It was still suspected that he had an infection and probably because of the sterile pyuria antituberculous treatment with Isoniazid and Ethambutol was initiated Apparently with negative PPD reaction was interpreted as possible anergy to the PPD because of the observed negative reaction to the mumps antigen In general with tuberculous infection present for approximately 6 weeks the PPD is positive with the exception of anergic states in severely debilitated patients or those patients who are on steroids The negative reaction to intermediate PPD would be much against tuberculosis here

When one sees an individual with unexplained fever especially if he has a pathologic murmur (which is not noted at any point in this protocol) one must consider infective endocarditis Negative blood cultures do occur in approximately 15 per cent of the cases of bacterial endocarditis especially in people infected with fastidious organisms which have to be grown under special conditions such as high CO_2 and special media The absence of a pathologic murmur is in my

Clinical pathologic conference

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Clinical summary

A 52 year old business executive was admitted to the hospital because of fever, night sweats malaise and weight loss At the age of 42 he first noted episodes of palpitations He was told he had paroxysmal atrial tachycardia, and was treated with digitalis He remained asymptomatic over the ensuing 8 years until a 3 week episode of refractory atrial tachycardia prompted his admission to the hospital At that time he was normotensive and had no other symptoms Physical examination chest x ray, and laboratory data were all interpreted as normal The electrocardiogram (ECG) was interpreted as atrial flutter with variable A V block Wenckebach phenomenon and depressed T waves in Leads I, aV_L V_5, and V_6 He was cardioverted placed on quinidine, and discharged in normal sinus rhythm Two years later, while on a business trip abroad he developed headaches and jaw pain which were not relieved by aspirin A dental examination and dental x rays were normal He was referred to a local physician with suspected angina pectoris ECG and serum enzyme studies were normal Shortly thereafter he developed a low grade fever, drenching night sweats and increasing malaise and fatigue He also began to lose weight and lost 25 pounds over a 6 week period

An evaluation for hepatitis was negative, and the chest x ray was interpreted as normal The urine sediment, however, contained numerous white cells and bacteria He was treated with Vibramycin without improvement in the fever or other symptoms

The patient was admitted to the hospital with a fever of unknown origin The temperature was 99 8° F, the pulse was 80 and regular and the blood pressure was 110/64 mm Hg On physical examination the PMI was in the fifth left intercostal space at the midclavicular line No murmurs were heard The first and second heart sounds were normal The liver was palpable 2 cm below the right costal margin, and several examiners felt that the splenic tip was palpable at the left costal margin The chest x ray was interpreted as within normal limits An ECG demonstrated a probable atrial rhythm with a rate of 65 biphasic P waves in the inferior leads and depressed T waves throughout An extensive laboratory workup to rule out infectious and malignant etiologies was negative The significant findings were the continued presence of numerous white blood cells in the urine sediment although urine cultures were repeatedly negative and there was a persistently elevated erythrocyte sedimentation rate Mumps and PPD skin tests were negative although the patient gave a history of mumps as a child Chest x rays intravenous pyelogram liver scan gastroscopy, collagen workup, bone marrow aspirate and temporal artery and scalene node biopsies were all normal Repeated blood cultures were negative One week after admission and withdrawal of all medications, an ECG demonstrated the reappearance of atrial flutter with variable block An echocardiogram suggested slight enlargement of the left atrium The patient was discharged 3 weeks after admission without a diagnosis

Although urine cultures for mycobacteria were still negative he was treated with Isoniazid and

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Fig 2 Serial chest x rays (A) July 1973 (B) August 1973 (C) September 1973 AFIP Neg 74 11561 1

valve in diastole With the proper technique one can show that in systole echoes disappear from behind the mitral valve and appear in the left atrium This is due to the fact that the myxoma is usually a mobile tumor on a pedicle On the other hand if the tumor is small enough so that it does not descend downward into the mitral orifice the myxoma would not be detected by echocardiogram If the tumor is sessile not mobile at all or invading the left atrial wall one may not have descent into the mitral orifice or left ventricle and therefore have a negative echocardiogram

The second peculiarity as far as left atrial myxoma is concerned is the long history of atrial arrhythmia Arrhythmia is uncommon with left atrial myxoma Frequently these patients have normal sinus rhythm up to the point where the myxoma has almost completely filled the left atrium causing extreme obstruction of pulmonary venous return and pulmonary hypertension a situation markedly unlike mitral stenosis Atrial arrhythmia in this case therefore is against the typical left atrial myxoma and suggests that there is something irritating the atrial wall

Before proceeding with this discussion I would like to look at the electrocardiograms and chest x rays

Dr. deCastro The ECG of May 29 1971 revealed atrial flutter with a 2 1 A V block with an approximate atrial flutter rate of 240 per minute The frontal plane mean QRS axis was +80 Following electrical cardioversion ST T wave changes consistent with quinidine effect are noted and an inverted P wave in Lead III would suggest a low atrial pacemaker with a P vector directed superiorly toward the left shoulder On July 20 1973 the ECG demonstrated atrial flutter with variable (2 1 3 1) ventricular response The ECG of Sept 25 1973 showed right axis deviation with a mean frontal plane axis of +110 nonspecific ST and T changes and slowing of the atrial rate to approximately 180 per minute with an associated 2 1 ventricular response The ST T wave changes are nonspecific and may be related to digoxin and quinidine effects The slowing of the atrial flutter rate from 240 to 180 per minute is probably secondary to quinidine The appearance of right axis deviation with a deep S wave in V_6 suggests right ventricular hypertrophy Right axis deviation can be the earliest evidence of right ventricular overload secondary to the development of pulmonary hypertension (see Figs 1 and 2)

Dr Cheitlin If one examines the x rays serially the development of a prominence in the area of the main pulmonary artery and the left atrial appendage is seen The first chest x ray looks perfectly normal The next x ray shows what appears to be a double density along the left heart border in the area of the left atrial appendage Whether this is an artefact of the film or is real I do not know at this point Especially in the last film there appears to be cardiomegaly involving the right ventricle and perhaps the right atrium consistent with the development of right heart failure possibly secondary to pulmonary hypertension Against this is the fact that no mention is made of an abnormal second sound The last ECG with right axis deviation would be consistent with pulmonary hypertension However the absence of any mention of dyspnea or orthopnea throughout the protocol suggests that what we are seeing on the left heart border is not

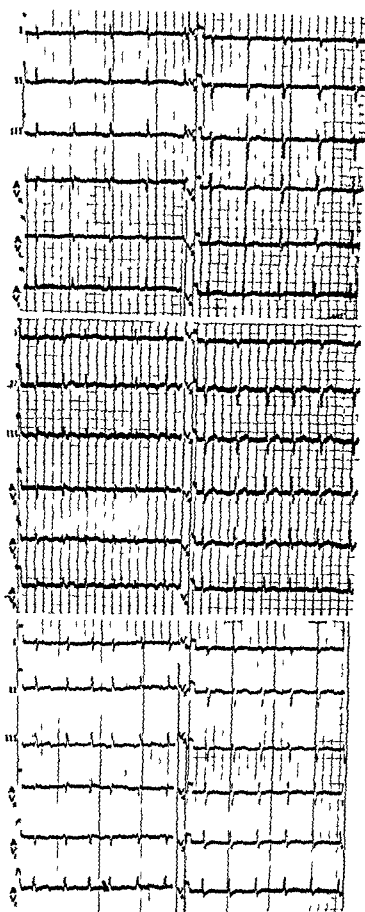


Fig 1 Serial ECG's The top tracing is following cardioversion in April 1971 the middle tracing was taken in July 1973 and the bottom tracing in *September 1973 AFIP Neg 75 1342*

experience, very much against infective endocarditis and at no time is a murmur described In drug addicts with acute endocarditis the patient may present without murmurs, and with tricuspid endocarditis may, indeed, remain without murmurs manifesting their disease solely by multiple pulmonary septic emboli There are some murmurs which are very difficult to hear, and which can be missed such as that of aortic insufficiency Indeed one can detect aortic insufficiency by angiography and not actually hear a murmur at the chest wall In instances of mitral stenosis where the right ventricle is dilated and the left ventricle is away from the chest wall, there may be no diastolic murmur audible at the apex, so called silent mitral stenosis , however these patients usually have a loud first heart sound and may have an opening snap with a loud pulmonic component of the second heart sound Apparently none of these findings was detected

We are left then, with an individual who has a systemic disease with an elevated erythrocyte sedimentation rate anemia increased gamma globulins on serum protein electrophoresis and as far as I can tell no embolic phenomena

In a patient with the clinical picture of infective endocarditis and persistently negative blood cultures one should always think of the most common tumor involving the heart—cardiac myxoma With myxoma in the left atrium the clinical picture is frequently that of infective endocarditis with low grade fever, embolic phenomena frequently polyclonal elevation of gamma globulins and murmurs which are changing because of the mobile tumor often with symptoms of mitral valve obstruction It is common with the left atrial myxoma not to have very much enlargement of the left atrium and as a matter of fact the absence of left atrial enlargement in a patient who has symptoms suggesting mitral stenosis is a point favoring the diagnosis of left atrial myxoma This patient has no symptoms such as dyspnea to suggest left atrial outflow obstruction

There are two other points unfavorable to the diagnosis of left atrial myxoma in this case One is that the echocardiogram which showed only minimal left atrial enlargement demonstrated no echoes behind the mitral valves in diastole which is against a mobile intra atrial cavitary mass Occasionally in a patient with left atrial myxoma, the echocardiogram can fail to show the characteristic shower of echoes behind the mitral



Fig 3 (A) The atrial septum in the region of the A V node is replaced by nodular tumor masses (arrow) (B) The tumor encased the outflow tract of the left ventricle The left coronary artery (arrow) although encased in tumor is patent AFIP Neg 75-1704

associated with atrial arrhythmias a prominent presenting feature of our patient s problem

The next most common tumors the lymphoma leukemia group are not intrinsic to the heart but are common neoplasms invading the heart I have no way of making this diagnosis from the protocol on this patient

Metastatic or locally invasive tumors such as bronchogenic carcinomas thymomas and malignant melanomas most frequently are silent invaders of the heart and are discovered post mortem without being suspected clinically Finally rhabdomyosarcomas may well be the most frequent primary tumors invading the myocardium and causing symptoms

To summarize because of the negative echocardiogram atrial arrhythmias which are a prominent part of this man s story disease of a very rapid onset without evidence of an etiologic infectious agent the peculiar masslike lesion in the area of the left atrial appendage and what I am interpreting as localized pulmonary venous obstruction I would favor the diagnosis of a

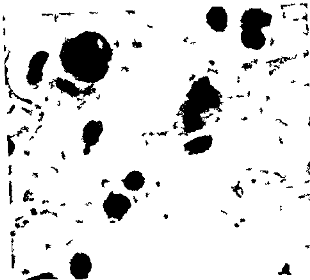


Fig 4 Racquet and strap cells from the tumor mass which although not diagnostic are suggestive of a rhabdomyosarcoma AFIP Neg 75 1705 (Hematoxylin and eosin ×1,200)

sessile cardiac tumor involving the left atrial wall and obstructing the pulmonary veins especially from the left lung It is possible that the neoplasm is invading the pericardium and causing restriction of ventricular filling and moderate pulmonary hypertension The only evidence of right heart failure that we have is a description of the liver which might be moderately enlarged and the apparent hepatic congestion on liver biopsy This would suggest systemic venous hypertension but I would certainly feel better with a description of the neck veins

It would be worthwhile to speculate upon the mode of death of this patient Perhaps the mechanism of death is that the tumor invaded the ventricular myocardium and caused sudden fatal ventricular fibrillation

Dr Fenoglio The liver biopsy obtained at laparotomy demonstrated both acute and chronic passive congestion The spleen and lymph node biopsies were unremarkable

At autopsy the pericardium was partially obliterated by dense adhesions Over the left atrium and at the base of the heart the pericardium was replaced by a large friable necrotic yellow white tumor mass The tumor extended along the pulmonary veins to the hilus of the left lung but neither invaded the walls of the veins nor the lung On transecting the heart at the base the tumor mass completely encircled the pulmonary artery and ascending aorta and compressed both the trachea and esophagus The tumor appeared

enlargement of either the left atrial appendage or the pulmonary artery, but something other than an enlarged cardiac or vascular structure

It is also striking on the chest films that there is pulmonary venous distension which is much more prominent on the left than on the right side This apparently involves not only the upper pulmonary veins which is the usual story with the development of pulmonary hypertension with mitral stenosis but also the inferior pulmonary veins mainly if not solely, on the left side This unilateral distension of pulmonary veins on the left side suggests that the pulmonary venous obstruction is not at the level of the mitral valve or left ventricle, but is at the local atrial level, perhaps at the entrance of the pulmonary veins into the left atrium

The obstruction of the pulmonary venous return from one lung would not account for pulmonary hypertension If this patient does, indeed have pulmonary hypertension and right heart failure, one must conclude that not only the pulmonary veins from the left lung but also some of the pulmonary veins from the right lung are involved In the protocol evidence for right heart failure is minimal Distension of the neck veins on physical examination is never mentioned, and only minimal liver enlargement and the hepatic congestion that was found on liver biopsy suggests that he had right heart failure

It is unfortunate that a lung scan was not done On lung scan, if there is a localized obstruction to pulmonary venous return from one lung a situation which we have seen before with tumor obstruction of the pulmonary venous return there is increased resistance to flow through the obstructed lung with absence or marked decrease of perfusion to the lung However flow through the unobstructed lung is normal or increased, and on pulmonary angiogram the pulmonary arteries to both lungs are normally patent Another problem that we have seen with intrathoracic tumor pertinent to this discussion is involvement of the pulmonary artery with neoplasm This might also interfere with blood flow to one lung We have seen a patient with Hodgkin s lymphoma which had encircled the main branches of the pulmonary artery causing peripheral pulmonary artery stenosis The acquired pulmonary artery obstruction caused right ventricular enlargement and was associated with the typical murmur of peripheral pulmonary stenosis which disappeared after radiation

Another possibility in our present case is that a tumor has grown around the heart inside or outside the pericardium and caused a restrictive or constrictive effect If this involved both right and left ventricles, then the ventricular filling pressures increase together, and, as is seen in constrictive pericarditis the decreased cardiac output usually prevents the pulmonary venous pressure from rising to levels which result in pulmonary edema In this circumstance the patient might present clinically with the effects of increased systemic venous pressure, that is, right heart failure One must also consider constrictive pericarditis in the differential diagnosis Atrial arrhythmias are quite frequently associated with chronic pericarditis By far the most common arrhythmia, in my experience, is atrial fibrillation In the majority of constrictive pericarditides a definite etiology is not found The most commonly identified organism is tuberculosis Histoplasmosis is another commonly associated etiologic agent Then there are a variety of other less commonly identified etiologies such as trauma, purulent pericarditis which organizes and causes constrictive pericarditis, and occasionally patients with idiopathic (so called benign') pericarditis develop constriction The ejection fraction as measured by the echocardiogram is frequently normal In this patient, constrictive pericarditis is unlikely in light of the localized mass lesion in the area of the pulmonary artery and the left atrium with the local pulmonary venous congestion

It is appropriate now to consider a cardiac neoplasm as the cause of our patient s problems It is possible to have not only a primary intrinsic cardiac tumor causing these findings but also an extrinsic tumor invading the heart Most common among these is bronchogenic carcinoma, and indeed the individual that I mentioned with pulmonary venous obstruction had a bronchogenic carcinoma which was growing in the angle between the entrance of the left pulmonary veins Tomography, as well as mediastinoscopy may be helpful in making the diagnosis when one suspects a mediastinal tumor invading the surface of the heart

The question now arises as to the type of tumor this could be The most common intrinsic cardiac tumor is cardiac myxoma Although these can be sessile, they usually are pedunculated and rarely involve the free wall of the atrium usually arising from the limbus of the fossa ovale and not usually

Fundamentals of clinical cardiology

Physical and radiologic examination of the lung in the evaluation of cardiac disease

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Many cardiac abnormalities will in one way or another affect the lungs Thus examination of the lung is an integral part of cardiac evaluation Left ventricular failure mitral valve disease and some rare diseases affecting the left atrium and/or pulmonary veins lead to pulmonary venous hypertension When the hydrostatic forces in the pulmonary capillaries exceed the opposing forces of colloid osmotic pressure fluid tends to accumulate in interstitial and alveolar lung spaces Fluid in the interstitial spaces interferes with oxygen diffusion leading to hypoxia This stimulates hyperventilation which corrects partially the lowered partial pressure of oxygen (Po_2) but leads to excessive washing out of carbon dioxide (CO_2) Pco_2 drops and respiratory alkalosis ensues With excessive accumulation of alveolar fluid ventilation is compromised so that with the decrease in Po_2 there is an increase in Pco_2 and a tendency toward respiratory acidosis[1,2] The work of respiratory muscles is increased in congestion *because of increased lung stiffness* (decreased compliance) and the occasionally coexistent bronchospasm (cardiac asthma)[4]

In the bedside evaluation of a cardiac patient attention should be paid to the pattern and rate of breathing and to specific physical signs in the lung that could help to identify the underlying heart disease

Rapid shallow breathing which may be the earliest sign of left ventricular failure is expected with parenchymal or interstitial lung disease and could be a clue to recent pulmonary embolism[2,3] A patient with normal quiet respiration is unlikely to have significant pulmonary venous congestion parenchymal lung disease or pulmonary embolism unless the respiratory *center is depressed* by disease or drugs and in this case arterial blood gases will indicate hypoventilation Severe bronchospasm manifest by prolonged labored expiration is occasionally seen with left sided heart failure and in pulmonary embolism[5,6] *It may be detected* at the bedside by observing the chest and abdominal muscle movements with respiration and can be confirmed by respiratory function tests Wheezing is not essential to make a diagnosis of bronchospasm

Cheyne Stokes respiration with phasic apnea alternating with hyperventilation is often seen in elderly people with left sided heart failure particularly with coexistent organic brain disease after analgesic drugs or even during deep sleep By *itself* this phenomenon does not have special significance nor does it require specific treat*ment*

In the intensive care area the decision to institute mechanical respiratory assistance often rests primarily on whether the patient exhibits clinical features of severe respiratory distress even if blood gases are reasonably well maintained[6] Working alae nasi frowning mouth breathing facial expression of distress sweating and restlessness are among features that indicate that the patient is fighting for his breath Assisted ventilation is *often recommended* under these circumstances before the patient exhibits exhaustion with deterioration in the general condition and blood gases

Asymmetry of the chest is most commonly due

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to arise from the left atrium and atrial septum and on opening the heart multiple tumor nodules bulged into both the left and right atria In the right atrium the tumor appeared to completely replace the region of the atrioventricular node The outflow tract of the left ventricle was completely encircled by the large tumor mass which had encircled but not compressed the left circumflex coronary artery The myocardium of the left ventricle was compressed by the tumor mass but did not appear to be invaded by tumor No spread of tumor into the right ventricle was noted All four cardiac valves appeared normal and were neither distorted nor invaded by the tumor The coronary arteries were in their normal location and, although surrounded by the tumor mass were widely patent and relatively free of atheromatous disease (see Figs 3 and 4)

Microscopically 95 per cent or more of the tumor was necrotic and only the most peripheral areas were well preserved In these areas the tumor was composed of extremely pleomorphic deeply eosinophilic cells The majority of the cells were small and rounded with pyknotic nuclei however there were numerous large bizarre cells and giant cells with two and three vesicular nuclei and prominent nucleoli Occasional strap cells both unipolar and bioplar and racquet cells, unipolar cells with a large nucleus at the expanded end and a thin tapering tail of eosinophilic cytoplasm, were present Although not prominent, faint cross striations were identified in these cells Mitotic figures were present although not numerous and fibrous tissue septae were prominent The tumor compressed, but did not invade either the ventricular myocardium or the His bundle in the region of the ventricular septum However, the A V node could not be identified on serial sections of multiple blocks from the anatomical region of the node This entire region was replaced by tumor

The mediastinal lymph nodes were the only sites of metastasis The remainder of the autopsy reflected only signs of cardiac failure The lungs were heavy and contained scattered heart failure cells and the liver was enlarged (3 000 grams) and congested There was no evidence of a lymphoma or of tuberculosis

This patient had a rhabdomyosarcoma of the heart, presumably arising in the atrial septum

Dr Cheitlin It is always encouraging to a clinician when the answer comes out right even if some of the assumptions made from the protocol were incorrect First, it is quite obvious that we should have commented about the fact that the atrial arrhythmia which he had 10 years before was probably unrelated to the pathology that finally caused his death The development of atrial flutter, on the other hand might well have been related to his primary tumor The other point has to do with whether or not there was indeed, pulmonary hypertension In order to have pulmonary hypertension as I said, the pulmonary veins of both lungs would have to be at least partially obstructed, it would not be sufficient to have the pulmonary veins of one lung obstructed by the tumor surrounding the base of the heart He may well not have had pulmonary hypertension, and actually may have had obstruction to filling of the right and left atrium as a result of the large tumor mass resulting in the signs of systemic congestion found at autopsy

Dr McAllister will you comment on your experience with primary sarcoma of the heart?

Dr McAllister Collectively, sarcoma is the second most common primary tumor of the heart In the AFIP series of 550 primary cardiac tumors myxoma was the most common (145 cases) followed by sarcoma (90 cases) Sarcomas may develop from any derivative of mesenchyme and occur most frequently in the right atrium and left atrium In our material the peak incidence was between 20 years and 50 years and males were affected approximately twice as frequently as females Only four of the 90 cases were under the age of 16 years Angiosarcoma fibrosarcoma and rhabdomyosarcoma were the most common types and occurred with almost the same degree of frequency Primary cardiac sarcomas may present either as intracavitary masses causing obstructive symptoms or intramural lesions resulting in arrhythmia or congestive heart failure, the initial presentation may be one of constitutional symptoms such as fever, anemia weight loss etc, without signs or symptoms referable to the heart

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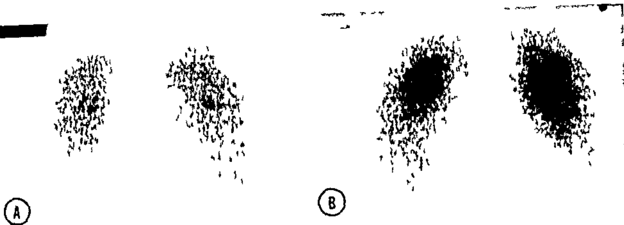


Fig 3 Anterior (A) and posterior (B) I macroaggregate albumin perfusion lung scan in a patient with pulmonary venous hypertension Note the redistribution of the radioisotope uptake toward the upper lung lobes and the relatively lesser perfusion of the lower lobes

films are shown in Fig 1 developed orthostatic hypotension severe sinus tachycardia and signs of low cardiac output on assuming the erect posture She improved following surgical correction of the sternal deformity Inspection of the chest wall for tender swollen joints rashes dilated veins and the like is an essential part of clinical examination

With a patient in acute respiratory distress it is important to note whether there is mediastinal shift In tension pneumothorax or massive pleural effusion the mediastinum shifts away from the side of disease which is indicated by limited respiratory chest movements The shift is toward the side of disease in lung collapse

The availability of radiographic examination of the chest has made it easy to detect early changes in the lung and pleura It has therefore minimized the value of percussion in the diagnosis of lung or pleural disease

Localized fixed rales that are not altered with breathing or cough suggest localized bronchial stenosis Râles limited to the left lower lung lobe are not uncommon in mitral valve disease because the enlarged left atrium compresses the left lower lobe bronchus making this lobe vulnerable to infection and inadequate drainage [4] In gross pericardial effusion there are often an impaired percussion note hollow breathing and rales in the left infrascapular region (Ewart's sign") presumably due to lung compression by the distended pericardial sac Bilateral basal lung râles are often sought as an indication of pulmonary venous congestion however their absence does not exclude heart failure nor does their presence confirm it Elderly patients those confined to bed and those with impaired cough reflex often retain bronchial secretions in the lower bronchi and therefore have rales

An audible pleural rub is a useful clinical sign of pleural involvement particularly when the chest film is equivocal

Murmurs heard over the chest may be propagated from the heart or originate from flow through vascular structures in the chest wall or the lungs Continuous murmurs indicate a communication between a systemic artery and either a relatively low pressure pulmonary artery or a vein Arteriovenous fistulas of the internal mammary or intercostal vessels arterial collaterals in coarctation of the aorta bronchopulmonary collaterals in pulmonary atresia systemic artery to pulmonary artery or vein fistula or anomalous origin of a stenotic pulmonary artery from a common truncus arteriosus give rise to continuous murmurs Stenoses of pulmonary artery branches do not produce murmurs in the absence of pulmonary hypertension Fig 2 shows an example of this in an asymptomatic 55 year old man with normal physical and electrocardiographic findings He had multiple peripheral pulmonary stenoses that were not sufficiently extensive to lead to elevated pulmonary pressure In patients with moderately severe pulmonary hypertension stenosis of a peripheral pulmonary artery produces a systolic murmur With severe pulmonary hypertension a continuous murmur is usually produced reflecting a continuous pressure gradient across the stenotic segment [21, 22]

Plain chest films reflect to a greater or lesser extent the degree of elevation of pulmonary



Fig 1 Severe funnel deformity of the chest There is severe depression of the lower third of the sternum compression of the right ventricle and displacement of the heart to the left



Fig 2 *A* Chest radiograph *B* pulmonary arteriogram Pulmonary artery coarctations discovered during a routine chest radiograph in a 55 year old man Note the multiple areas of narrowing with poststenotic dilatation of the affected branches

to scoliosis of the spine Developmental abnormalities of the sternum are not uncommon in patients with congenital heart disease notably septal defects [10] A bulging precordial area with retraction at the site of diaphragmatic insertion is characteristic of a large ventricular septal defect associated with considerable pulmonary hypertension [11] Depression of the lower third of the sternum is often seen with the Marfan s syndrome and its incomplete forms [12] Severe pectus excavatum deformity may occasionally be responsible for hemodynamic embarrassment with decrease in cardiac output particularly in the upright position [13,14] The patient whose chest



Fig 6 Alveolar pulmonary edema in a patient with acute hypersensitivity reaction Note the patchy nature of the lung shadows



Fig 8 Atrial septal defect with increased pulmonary blood flow Note the enlargement of the main pulmonary vessels and the prominent primary secondary and tertiary branches



Fig 7 Alveolar pulmonary edema in a uremic patient Note the batwing distribution and the fluffy nodular densities

3 *Alveolar edema* Perhaps all patients with pulmonary venous congestion have more or less alveolar edema Excessive alveolar edema is seen with rapidly progressive left ventricular failure with the onset of atrial fibrillation in a patient with mitral stenosis or when there is extensive damage to the pulmonary capillary bed Typically there is diffuse opacification of the hilar and lower lung zones (batwing appearance) with hazy margins Air bronchograms are seen in the opacified zones (Fig 5) Edema may have nodular or patchy distribution initially [3] before it takes the typical distribution should the patient survive for a few days (Fig 6)

4 *Pleural edema* Typically in a congested lung the interlobar fissures are edematous and can be seen easily in the chest films Unilateral or bilateral pleural effusions are common and may be free and/or loculated

Pulmonary edema is enhanced by decreased plasma colloid osmotic pressure increased blood volume and increased pulmonary capillary permeability such as is encountered with low atmospheric Po pulmonary infections and exposure to irritative gases [1,3] Pulmonary edema may be massive in uremic patients because of the interplay of many of the aforementioned factors in addition to left ventricular failure (Fig 7)

The clearance of lung shadows with diuretic therapy (allowing for a time lag) is further retrospective evidence that those particular lung shadows had been due to heart failure



Fig 4 Interstitial pulmonary edema and venous hypertension in a patient with severe mitral valve stenosis Note the Kerley B lines (arrow) the engorgement of the upper lobe vessels and vasoconstriction of lower lobe vessels



Fig 5 Alveolar pulmonary edema with typical batwin distribution in a patient with aortic valve stenosis This is not an infrequent radiographic appearance of pulmonary edema in left heart failure

venous pressure[23,24] With left atrial pressures in excess of 15 mm Hg there is dilatation of upper lobe veins and of the distribution of pulmonary artery blood flow so that the upper lung lobes receive relatively more blood flow than the lower lobes[24,26] This finding is more pronounced in ambulatory patients when the chest films are taken in the upright position than in those taken with the patient flat in bed[27] Reversal of pulmonary flow probably relates to the fact that with a left atrial pressure of 15 mm Hg the upper lobe veins receive a pressure of less than 10 mm Hg while the lower lobe veins are subjected to a pressure of more than 20 mm Hg, the differential being due to the influence of gravity It is believed that with interstitial edema developing in the lower lung zones, there is a drop in blood Po_2 and pH in the lower pulmonary venules which presumably excites a local chemoreceptor reflex that leads to constriction of the corresponding muscular pulmonary arteries[28,29] Fig 3 shows a perfusion lung scan from a patient with early left ventricular failure demonstrating increased blood flow to the upper lung zones

Higher pulmonary venous pressures lead to pulmonary edema which is manifest by[7] the following characteristics

1 *Perivascular and peribronchial edema* Pulmonary vessels are ill defined and are surrounded by a diffuse haze while bronchial air spaces contrast with the surrounding cuffings of edema

2 *Interstitial edema* There is general decrease in lung lucency, especially in the hilar regions and lower lung zones

The hallmark of interstitial lung edema is Kerley lines[30] Kerley A' lines are straight unbranching lines that extend from the hila to the upper lung zones They are most often seen with acute left ventricular failure Kerley B lines (Fig 4) are more specific for pulmonary venous congestion These are horizontal lines seen in the lower lung zones especially in the costodiaphragmatic angles Initially, these lines represent interstitial edema and therefore can be made to disappear with diuretic treatment With long standing pulmonary venous hypertension interstitial fibrosis develops and these lines become permanent even after treatment of the cause of pulmonary venous congestion (such as after successful mitral valve commissurotomy) Kerley C lines are fine curvilinear shadows seen in the middle and lower lung zones They are of no substantial diagnostic value as they could be seen with interstitial lung fibrosis due to almost any cause



Fig 12 Mild pulmonary oligemia in moderately severe pulmonic valvar stenosis Severe oligemia is seldom observed in this condition in the absence of a right to left shunt



Fig 13 Pulmonary oligemia in tetralogy of Fallot

vasculature (Fig 12) Features of pulmonary oligemia with decreased diameter of all components of the pulmonary arterial tree are typically seen in severe Fallot s tetralogy (Fig 13) In that case bronchopulmonary collaterals are often identified by their reticular pattern or as fine linear shadows running parallel to the bronchi[37]

Pulmonary infection segmental atelectasis and various lung complications are common in cardiac patients with pulmonary venous congestion Infective endocarditis of the right side of the heart is seen in heroin addicts and occasionally as a complication of congenital heart disease such as ventricular septal defect or patent ductus arteriosus In these cases patients often present with recurrent pulmonary infarctions abscesses or bronchopneumonia

Pulmonary embolism is usually suspected in a clinical setting[7] but confirmation may require perfusion lung scans and/or pulmonary angiography[14] The electrocardiogram is abnormal in a minority of cases and the abnormalities are often nonspecific Likewise findings in chest films suffer from incomplete sensitivity and lack of specificity

Perfusion lung scans can be obtained by intravenous injection of [131]I macroaggregated albumin or technetium[99m] albumin microspheres (Fig 14) Perfusion scans have a high degree of sensitivity and specificity particularly if interpreted in the light of clinical data and information from plain chest films Xenon 133 ventilation lung scans can be combined with perfusion scans to further enhance the value of the latter in establishing the diagnosis of pulmonary embolism[7]

Perfusion lung scans can be difficult to interpret in patients with underlying chronic lung disease or left ventricular failure and when the scans show subsegmental or ill defined perfusion defects limited to the lower lung lobes[4] Under those circumstances pulmonary angiography may be required to establish the diagnosis (Fig 15) Pulmonary angiography is also required before major surgical procedure on the inferior vena cava[8] if surgical removal of pulmonary emboli is contemplated and preferably before the institution of fibrinolytic therapy

Conclusions

The bedside evaluation of heart disease requires attention to the rate and pattern of



Fig 9 Oligemia of the right lung and shunt vascularity of the left lung in a patient with the scimitar syndrome The anomalous pulmonary vein is seen through the cardiac density to the right of the sternum (arrow)



Fig 11 Chest film of a patient with schistosoma pulmonary hypertension There is aneurysmal dilatation of the main pulmonary artery and its main branches

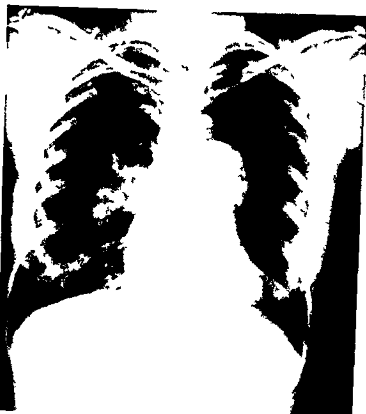


Fig 10 Severe pulmonary arterial hypertension in a patient with patent ductus arteriosus Note the markedly dilated main pulmonary branches with decreased vascularity in the middle and outer thirds of the lung fields

Increased pulmonary flow is less easy to diagnose from a chest film unless the increase in pulmonary flow is substantial As an example patients with a left to right shunt and pulmonary flow less than twice systemic flow may not exhibit clear cut radiologic evidence of pulmonary plethora'[31] Increased pulmonary flow is reflected in increase of the diameter of the main primary, secondary, and tertiary pulmonary arterial branches (Fig 8)

Occasionally anomalous venous drainage can be identified from a chest film In the scimitar syndrome the right pulmonary veins drain into the inferior vena cava, below the diaphragm, via a large sword shaped venous channel (Fig 9) There is also hypoplasia of the right pulmonary artery and the hypoplastic right lung is usually supplied by anomalous arteries from the aorta[32, 33]

In pulmonary hypertension there is marked attenuation of the pulmonary vessels in the outer third and even the middle third of the lung fields[34] This contrasts with dilatation of the main pulmonary artery and its primary branches (Fig 10) Such dilatation may attain aneurysmal proportions, especially in patients with schistosoma pulmonary hypertension[35] In this disease *Schistosoma mansoni* worms live in the portal veins, and the ova embolize small pulmonary arteries, producing endarteritis and perivascular granuloma leading eventually to severe pulmonary hypertension Of 46 patients with schistosoma pulmonary hypertension studied by Basta and co workers[36] 30 showed aneurysmal dilatation of the proximal pulmonary arteries (Fig 11)

Patients with mild to moderate stenosis of the pulmonic valve usually have normal pulmonary



Fig 15 Pulmonary embolism and infarction A Chest radiograph showing oligemia of both upper lung zones causing increased transradiancy (Westermark s sign in pulmonary embolism) The pleural based infiltrate in the left lower lobe is probably an infarct B Pulmonary arteriogram of the same patient in the arterial phase showing a huge saddle embolus obstructing partially the right upper and middle lobe arteries Multiple filling defects are seen within the smaller branches of the left pulmonary artery

attenuated distal vessels Pulmonary oligemia is seen with severe pulmonic stenosis and Fallot s tetralogy

Infective endocarditis of the right side of the heart often presents with multiple pulmonary infections and/or infarctions Pulmonary embolism is usually suspected from clinical laboratory electrocardiographic and plain chest film findings The diagnosis can be established from perfusion lung scans and/or pulmonary angiograms Angiography is required in patients with underlying heart failure or chronic lung disease when perfusion scans show ill defined basal defects and before pulmonary embolectomy or surgical procedure on the inferior vena cava

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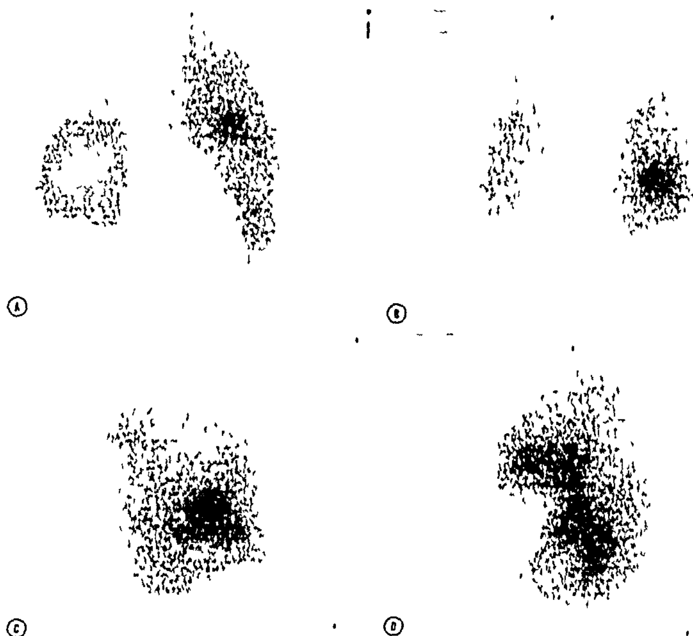


Fig 14 Anterior (*A*) posterior (*B*) right (*C*) and left (*D*) lateral ¹³¹I macroaggregated albumin lung scans in a patient with multiple pulmonary emboli Note the diminished perfusion at the right upper lobe at the apical and posterior segments of the right lower lobe at the posterior segment of the left upper lobe and at the lingula

respiration and whether there are signs of respiratory distress or bronchospasm Deformity of the sternum and chest wall is seen in pectus excavatum, and commonly in Marfan s syndrome and with congenital heart disease Râles over the left lower lung lobe are often heard in mitral stenosis Basal lung rales may be absent in left ventricular failure and are heard often in the elderly or those confined to bed, regardless of whether there is pulmonary congestion Examination of the chest should include search for murmurs with emphasis on whether they are propagated from the heart Continuous murmurs indicate a communication between a systemic artery and a vein or low pressure pulmonary artery Peripheral pulmonary artery stenosis may be silent in the absence of pulmonary hypertension but may give a systolic or even a continuous murmur with elevated pulmonary artery pressure

Radiologic features of pulmonary venous congestion include increased perfusion of upper lung zones and transudation in the interstitial and alveolar spaces in hilar and lower lung zones as well as in pleural spaces

Increased pulmonary flow such as with large left to right shunts leads to prominent vascular markings but no edema Anomalous venous drainage is often diagnosed from a plain chest film Pulmonary hypertension is characterized by prominent proximal pulmonary branches and



Fig 15 Pulmonary embolism and infarction *A* Chest radiograph showing oligemia of both upper lung zones causing increased transradiancy (Westermark's sign in pulmonary embolism) The pleural based infiltrate in the left lower lobe is probably an infarct *B* Pulmonary arteriogram of the same patient in the arterial phase showing a huge saddle embolus obstructing partially the right upper and middle lobe arteries Multiple filling defects are seen within the smaller branches of th left pulmonary artery

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Electrophysiology and pharmacology of cardiac arrhythmias VIII Cardiac effects of diphenylhydantoin A

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Diphenylhydantoin (DPH) a structural analog of the barbiturates was introduced into clinical medicine as an anticonvulsant by Merritt and Putnam in 1938[1] Its principal use today is still for the treatment of epilepsy The idea for its use as a cardiac antiarrhythmic drug originated in 1950 when Sidney Harris speculated that the mechanism of origin of cardiac arrhythmias due to myocardial infarction might be similar to that of epileptiform seizures It was believed that epileptic seizures were generated by the flow of current at the border between injured necrotic brain tissue and normal tissue Because in myocardial infarction necrotic and normal heart muscle are adjacent to one another Harris investigated the effects of DPH on arrhythmias in dogs after experimental infarction and found it to be particularly effective Subsequent studies on arrhythmias induced in animals by a variety of techniques also demonstrated that DPH had a significant antiarrhythmic effect[3]

It was not until 1958 that DPH was used clinically At this time Leonard successfully treated with DPH a case of ventricular tachycardia refractory to quinidine and procaine amide This result prompted a substantial investigation of the effects of DPH on clinical cardiac arrhythmias

I Antiarrhythmic effects of DPH

Atrial arrhythmias not due to digitalis toxicity DPH is ineffective against atrial arrhythmias which result from causes other than digitalis toxicity Although a small percentage of cases of atrial tachycardia has responded to DPH most atrial tachycardias premature atrial contractions and cases of atrial flutter and fibrillation are not affected[8-11] DPH on occasion may slow the ventricular response during atrial flutter or fibrillation[1] but the occurrence of this effect is unpredictable and DPH is not used clinically for this purpose

Atrial arrhythmias resulting from digitalis toxicity In contrast to its lack of effectiveness against atrial arrhythmias associated with acute or chronic cardiac disease DPH is highly effective against the atrial arrhythmias which result from digitalis intoxication[12] Supraventricular tachycardia and paroxysmal atrial tachycardia with and without atrioventricular block have been converted to sinus rhythm in the majority of reported cases[1] Paroxysmal atrial fibrillation and atrial flutter also respond well to DPH and may be converted to sinus rhythm AV junctional rhythms or tachycardias are more resistant to antiarrhythmic therapy with DPH as well as with other antiarrhythmic drugs

Ventricular arrhythmias associated with ischemic heart disease The efficacy of diphenylhydantoin in the treatment of ventricular premature contractions and ventricular tachycardia resulting from ischemic heart disease is uncertain because of the inconsistent results of reported studies When administered for acute arrhythmias resulting from myocardial infarction DPH is sometimes effective in abolishing or reducing the frequency of ventricular ectopic beats[8,9,13] However successful use of DPH in this clinical situation is modest when compared to the reported efficacy of lidocaine[5] DPH has been ineffec

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tive when administered prophylactically in attempts to prevent sudden death or recurring ventricular arrhythmias due to ischemic heart disease[14, 16]

There are several factors which may be responsible for the variability in the reported efficacy of DPH against ventricular arrhythmias associated with ischemic heart disease Effectiveness of an antiarrhythmic drug is predicated on its reaching and maintaining adequate concentrations at its site of action (as mirrored by plasma drug concentrations) Bigger and colleagues[8] have stressed that DPH is rarely effective in plasma concentrations less than 10 µg/ml and in several series which reported DPH to be ineffective plasma drug levels were not determined[9, 16] The possibility therefore exists that drug levels were inadequate

Another possible explanation for the ineffectiveness of DPH in some instances of arrhythmias accompanying myocardial ischemia may be the wide range of electrophysiologic mechanisms responsible for such arrhythmias For example, the mechanisms for arrhythmias occurring immediately after a coronary occlusion (prehospital phase) may differ from those present 12 to 24 hours later (in hospital phase) or from chronic arrhythmias which persist for months or years after infarction[17] In some instances DPH was found effective in the treatment of the acute in hospital arrhythmias resulting from myocardial infarction[8, 9, 13] In eight of the ten cases described by Stone and associates[14] the recurrent ventricular tachycardia which was refractory to DPH therapy resulted from myocardial infarction which had occurred 2 to 14 months previously The difference in the time of occurrence of these arrhythmias suggesting different underlying electrophysiological mechanisms, may be the basis for the differences in antiarrhythmic drug efficacy Still different underlying mechanisms may be responsible for the prehospital arrhythmias which may cause sudden death and may in turn explain the ineffectiveness of DPH in Lovell s study[16]

Ventricular arrhythmias associated with digitalis toxicity There is widespread agreement that diphenylhydantoin is highly effective against digitalis induced ventricular arrhythmias including bigeminy unifocal and multifocal ventricular premature contractions, and ventricular tachycardia[8, 10, 13, 18, 20] Up to 92 per cent of such ventricular arrhythmias have been reported to respond favorably to DPH[10] When used for digitalis induced ventricular arrhythmias, DPH does not appear to significantly impair AV nodal His Purkinje or ventricular muscle conduction also detrimental hemodynamic effects are rare[1] Because of its effectiveness, and a lack of toxic effects in this clinical setting it has been advocated that DPH be used preferentially to treat digitalis induced arrhythmias[1, 19] That lidocaine is actually the preferred antiarrhythmic drug treatment here probably reflects its greater ease of administration and the shorter duration of its toxic effects, should they occur

Ventricular arrhythmias with other etiologies Other arrhythmias which have been reported to respond favorably to DPH are those resulting from general anesthesia,[9, 11, 21] cardiac catheterization, and radiopaque dye injection[9] Ventricular arrhythmias occurring during or after cardiac surgery have been successfully treated with DPH[8, 9, 2, 23] as have those following DC cardioversion of atrial arrhythmias[9, 11]

II Clinical pharmacology Plasma levels administration and pharmacokinetics

Plasma levels For DPH to exert its antiarrhythmic effects an adequate amount of drug must reach the site in the heart responsible for the arrhythmia Although the cardiac DPH concentration cannot be measured routinely, plasma DPH levels are a valid indicator of the cardiac concentration of the drug when plasma and tissue DPH concentrations are at or near equilibrium At this time the concentration in the heart is approximately equal to that in the plasma[24] Approximately 85 per cent of the plasma DPH is bound to plasma proteins and plasma DPH measurements include both the bound and unbound drug It is possible that at least some of the protein bound drug may be unable to exert electrophysiological effects on the heart The exact concentration of active drug is unknown

DPH also enters other tissues of the body The concentrations in the liver and adipose tissue are significantly higher than in plasma while the concentrations in the brain and kidney are approximately equal to that of the plasma[1]

DPH plasma levels of 10 to 18 µg/ml are regarded as the therapeutic range[8] although some

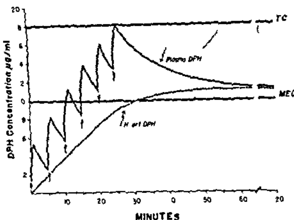


Fig 1A Estimated plasma and cardiac DPH concentrations *(ordinate)* during intravenous administration of 100 mg every 5 minutes *(abscissa)* DPH is administered at each arrow The solid trace indicates the plasma DPH level and the dashed trace the DPH concentration in the heart With each injection plasma level rises to a peak and then begins to decline prior to the next injection Each subsequent injection of DPH causes a further increase in the DPH plasma level until after three injections the plasma level enters the therapeutic range (indicated by the shaded area) (MEC = minimum effective concentration TC = toxic concentration) The DPH level in the heart increases more gradually After the sixth DPH injection drug administration every five minutes is discontinued Plasma level declines gradually as more drug enters the peripheral tissues including the heart (note that the cardiac DPH is still rising) but plasma level remains in the therapeutic range for a long time Now DPH need be administered less frequently to maintain these therapeutic plasma levels

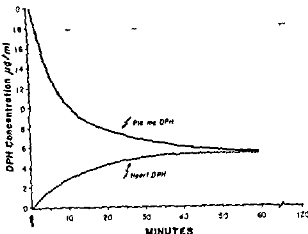


Fig 1B Estimated plasma and cardiac DPH concentrations *(ordinate)* after a single intravenous injection of 500 mg at the arrow The solid trace indicates the plasma DPH level and the dashed trace the DPH concentration in the heart After a single injection plasma level reaches 30 µg/ml almost immediately DPH has not had time to enter the heart so heart level of DPH is still low and there is no antiarrhythmic effect The subsequent decline in plasma DPH occurs as the drug enters the tissues of the body including the heart heart level of DPH is increasing. Plasma level of DPH falls below the therapeutic level after 10 minutes and heart level of DPH never reaches this therapeutic range As a result a single dose may not exert an antiarrhythmic effect

cardiac arrhythmias particularly those resulting from digitalis toxicity may respond to lower plasma levels Still higher plasma levels may occasionally be effective against other arrhythmias In general arrhythmias which do not respond to plasma concentrations of about 20 µg/ml will not respond to higher levels

Undesirable neurological effects begin to appear at plasma DPH concentrations of 20 µg/ml At this level blurred vision and nystagmus occur and at 30 µg/ml truncal ataxia and unsteadiness of gait become obvious Most patients become extremely lethargic at plasma DPH levels above 40 µg/ml.[25]

Administration DPH may be administered by either the intravenous or oral route Intramuscular administration is not used because absorption by this route is erratic and plasma drug levels are unpredictable In addition intramuscular DPH can cause tissue necrosis and sterile abscesses due to the high alkalinity of the solution [2]

For emergency treatment of cardiac arrhythmias intravenous DPH administration can rapidly achieve adequate plasma levels Bigger and associates have demonstrated a regimen for intravenous DPH administration which can be used to attain therapeutic plasma levels rapidly and safely Fifty to 100 mg of DPH is administered every five minutes until the arrhythmia is abolished until 1 000 mg has been given or until undesirable effects appear This method of administration results in a step wise increase in the plasma levels by 3 to 4 µg/ml after each dose as well as a gradual increase in DPH levels in the peripheral tissues (Fig 1A) This method allows establishment of the minimal effective plasma levels for arrhythmias responsive to DPH Once the effective antiarrhythmic plasma level has been achieved supplemental doses of DPH still are necessary to maintain the levels in the therapeutic range although they need be given less frequently than during initial therapy Usually if a total dose of 1 000 mg is given over the first 24

Table I Dosage schedule for DPH therapy*

	Day 1	Day 2	Day 3
Intravenous	1000 mg	500 mg	400 500 mg
Oral	1000 mg	500 mg	400 500 mg

* Each value is total daily dose

hours 500 mg can be given the second day to maintain plasma levels and smaller doses on subsequent days (Table I)[8] Maintenance doses can be given either intravenously or orally DPH should not be given as a constant intravenous infusion since the high alkalinity necessary to maintain DPH in solution may cause intense pain and thrombosis at the infusion site

Other methods of intravenous DPH administration have been used but these are not as effective and result in considerably more risk of toxic effects For example if 200 to 500 mg of DPH is administered over a few minutes as sometimes has been recommended very high plasma levels (reaching 30 μg/ml or more) occur within a short time and then rapidly decline to 4 to 8 μg/ml within 20 to 40 minutes (Fig 1*B*)[8, 27] The initial high concentration of DPH in the plasma may not be associated with a sustained antiarrhythmic effect for immediately after injection very little drug has had the opportunity to enter the heart The rapid fall in plasma concentrations which occurs over the first 30 to 40 minutes (Fig 1*B*) is probably due to continued uptake of DPH into the tissues[8] The plasma levels of 4 to 8 μg/ml which occur at a time when cardiac DPH concentrations are reaching equilibrium with the plasma may be inadequate for treatment of many cardiac arrhythmias In addition to the failure in achieving satisfactory antiarrhythmic levels by this method of administration, the administration of such a large amount of drug over a short period of time may cause significant hypotension due to a direct effect on the peripheral arterioles[28]

DPH can be administered orally with good results because the drug is nearly completely absorbed from the gastrointestinal tract Absorption is fairly slow however, and maximum plasma level after a single oral dose is achieved only after 8 to 12 hours[24] When administered without an initial loading dose, 300 to 500 mg /day usually will result in steady state therapeutic plasma levels of 10 to 20 μg/ml within 5 to 15 days [5] The occurrence of such a long period of time prior to attaining steady state levels (which indicate that a balance between drug intake and elimination has been established) is due to the slow metabolism and long half time for drug elimination

Obviously this oral regimen is unsatisfactory for the in hospital therapy of serious cardiac arrhythmias because of the long delay prior to attaining an adequate plasma concentration A more satisfactory dosage regimen is similar to the intravenous dose schedule (Table I) Administration of 1 000 mg of DPH orally on day 1 followed by doses of 500 to 600 mg on the second and third days and then maintenance doses of 400 to 500 mg /day provides adequate control of responsive arrhythmias within 24 hours and sustained therapeutic plasma concentrations[8] The large amount of DPH given on the first day probably results in high drug concentrations in the peripheral tissues and the 400 to 500 mg given after the second day are sufficient to replace metabolized DPH and maintain plasma levels

Metabolism Only 1 to 5 per cent of the DPH in the body is excreted unchanged by the kidneys[29] Inactivation of the remaining drug results from metabolism in the liver by the mixed function oxidase system The main biochemical alteration of the DPH molecule which occurs in the liver is hydroxylation of one of the phenol rings resulting in the formation of 5 phenyl 5 parahydroxyphenylhydantoin (HPPH) This is conjugated with glucuronic acid or sulfate and excreted in the urine[30, 31] Urinary excretion of HPPH can be measured and such measurements have valuable clinical applications Since many factors may alter the rate of DPH metabolism, leading to abnormally low or high DPH plasma levels (see below) low or high values for urinary HPPH may be indicative of such altered metabolism[3]

The amount of DPH hydroxylated increases linearly with the amount presented to the liver until, at a certain drug concentration the enzyme system is saturated[32, 33] Most patients can metabolize 10 mg /Kg or more DPH daily [5] Any increase in the amount of drug presented to the liver above the concentration which saturates the enzyme system does not result in an increase in the amount of drug metabolized per unit time (Fig 2) This behavior of the enzyme system responsible for DPH metabolism is extremely important in determining the relationship between the amount of drug given and the resulting plasma levels[33]

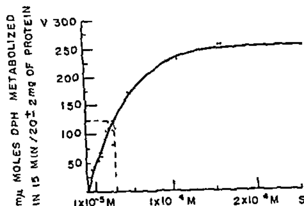


Fig 2 Dependence of DPH metabolism by liver enzymes on substrate concentration Data are from a study of metabolism of DPH by an isolated microsomal enzyme system as described by Kutt and Verebely The concentration of DPH added to a fixed quantity of enzym is on the *abscissa* and the amount of DPH metabolized is on the *ordinate* As the DPH concentration is increased from 1 × 10 to 1 × 10 M the amount of DPH metabolized increases. However further increases in DPH concentration eventually saturate the enzyme system and the amount of DPH metabolized per unit time reaches a steady level at about 1 5 × 10 M A further increase in DPH concentration now does not result in any further increase in metabolic rate (Reproduced from Kutt and Verebely Metabolism of diphenylhydantoin by rat liver microsomes I Characteristics of the reaction Biochem Pharmacol. 19 675 1970 Reproduced by permission)

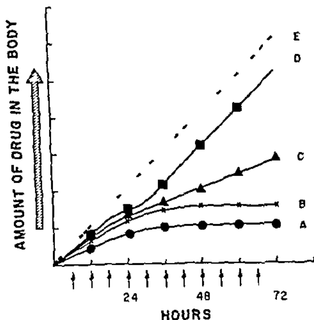


Fig 3 Possible effects of increasing the amount of drug administered on plasma drug le els when drug elimination occurs by first order kinetics dose-dependent kinetics and zero order kinetics Amount of drug in the body is shown on the *ordinate* and time on the *abscissa* For curve *A* an equal amount of a drug (which is eliminated by first order *kinetics)* is being administered orally every six hours as a *single dose (at the arrows)* Plasma level gradually increases and a plateau level is reached when the amount of drug eliminated equals the amount administered For curve *B* the amount of the drug administered every six hours is increased but the t½ *for* elimination remains the same Plasma level now increases to a higher value before a plateau level is reached For curve *C* the amount of the drug administered every six hours is increased further and at a critical plasma level the t½ for elimination now becomes prolonged (so-called dose-dependent elimination) A plateau level for the drug is not *attained within the* 72 hours shown on the graph instead the plasma level *continues* to rise For curve *D* the amount of drug administered every six hours is increased still further and now the metabolizing enzyme system becomes saturated Elimination now follows zero order kinetics and the plasma level rises precipitously Th dashed line *E* shows the predicted plasma levels if there were no drug elimination (zero order kinetics at all dose levels)

During initial intravenous administration of DPH the plasma levels may be linearly related to the number of 100 mg doses given by the method of Bigger and associates[4] and readily predictable At this time the characteristics of drug inactivation by metabolism are not important in determining plasma levels However when DPH is administered for several days or more the rate of drug metabolism is an important determinant of plasma levels and it may be more difficult to predict the amount of drug in the *plasma on* the basis of the amount administered *If drug elimi*nation follows first order kinetics (as is true for lidocaine procaine amide etc) *a schedule of* administration that will maintain a satisfactory plasma concentration can be estimated from the apparent volume of distribution and the t½ for elimination For such drugs the amount of drug eliminated per unit time is a fixed percentage of the total body store Increasing the amount of drug given results in a predictable rise in plasma concentration and drug elimination (Fig 3) DPH elimination has been described as being dose dependent[3] It shows apparent first order kinetics at low plasma levels (< 5 to 10 μg/ml) but the t½ for elimination becomes progressively longer at high plasma levels (> 5 to 10 μg/ml) until elimination shows zero order kinetics (Figs 4 and 5)[3] This occurs when there is enough DPH in the plasma to saturate the liver enzyme system and the rate of drug metabolism becomes fixed at a maximum value At this time if the dosage is increased none of the additional DPH may be metabolized and plasma levels may rise precipitously (Fig 3)[3] This means that when DPH

Table I Dosage schedule for DPH therapy*

	Day 1	*Day 2*	*Day 3*
Intravenous	1000 mg	500 mg	400 500 mg
Oral	1000 mg	500 mg	400 500 mg

*Each value is total daily dose

hours 500 mg can be given the second day to maintain plasma levels and smaller doses on subsequent days (Table I)[8] Maintenance doses can be given either intravenously or orally DPH should not be given as a constant intravenous infusion since the high alkalinity necessary to maintain DPH in solution may cause intense pain and thrombosis at the infusion site

Other methods of intravenous DPH administration have been used but these are not as effective and result in considerably more risk of toxic effects For example, if 200 to 500 mg of DPH is administered over a few minutes as sometimes has been recommended very high plasma levels (reaching 30 μg/ml or more) occur within a short time and then rapidly decline to 4 to 8 μg/ml within 20 to 40 minutes (Fig 1B)[8, 27] The initial high concentration of DPH in the plasma may not be associated with a sustained antiarrhythmic effect for immediately after injection very little drug has had the opportunity to enter the heart The rapid fall in plasma concentrations which occurs over the first 30 to 40 minutes (Fig 1B) is probably due to continued uptake of DPH into the tissues[8] The plasma levels of 4 to 8 μg/ml which occur at a time when cardiac DPH concentrations are reaching equilibrium with the plasma may be inadequate for treatment of many cardiac arrhythmias In addition to the failure in achieving satisfactory antiarrhythmic levels by this method of administration the administration of such a large amount of drug over a short period of time may cause significant hypotension due to a direct effect on the peripheral arterioles [*]

DPH can be administered orally with good results because the drug is nearly completely absorbed from the gastrointestinal tract Absorption is fairly slow, however and maximum plasma level after a single oral dose is achieved only after 8 to 12 hours[24] When administered without an initial loading dose 300 to 500 mg /day usually will result in steady state therapeutic plasma levels of 10 to 20 μg/ml within 5 to 15 days[25] The occurrence of such a long period of time prior to attaining steady state levels (which indicate that a balance between drug intake and elimination has been established) is due to the slow metabolism and long half time for drug elimination

Obviously this oral regimen is unsatisfactory for the in hospital therapy of serious cardiac arrhythmias because of the long delay prior to attaining an adequate plasma concentration A more satisfactory dosage regimen is similar to the intravenous dose schedule (Table I) Administration of 1 000 mg of DPH orally on day 1 followed by doses of 500 to 600 mg on the second and third days and then maintenance doses of 400 to 500 mg /day provides adequate control of responsive arrhythmias within 24 hours and sustained therapeutic plasma concentrations[8] The large amount of DPH given on the first day probably results in high drug concentrations in the peripheral tissues and the 400 to 500 mg given after the second day are sufficient to replace metabolized DPH and maintain plasma levels

Metabolism Only 1 to 5 per cent of the DPH in the body is excreted unchanged by the kidneys[5] Inactivation of the remaining drug results from metabolism in the liver by the mixed function oxidase system The main biochemical alteration of the DPH molecule which occurs in the liver is hydroxylation of one of the phenol rings resulting in the formation of 5 phenyl 5 parahydroxyphenylhydantoin (HPPH) This is conjugated with glucuronic acid or sulfate and excreted in the urine[30, 31] Urinary excretion of HPPH can be measured and such measurements have valuable clinical applications Since many factors may alter the rate of DPH metabolism leading to abnormally low or high DPH plasma levels (see below) low or high values for urinary HPPH may be indicative of such altered metabolism[3]

The amount of DPH hydroxylated increases linearly with the amount presented to the liver until at a certain drug concentration the enzyme system is saturated[33, 34] Most patients can metabolize 10 mg /Kg or more DPH daily[5] Any increase in the amount of drug presented to the liver above the concentration which saturates the enzyme system does not result in an increase in the amount of drug metabolized per unit time (Fig 2) This behavior of the enzyme system responsible for DPH metabolism is extremely important in determining the relationship between the amount of drug given and the resulting plasma levels[5]

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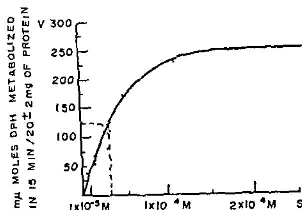


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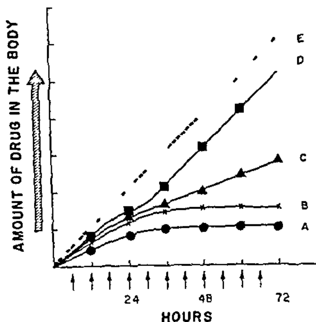


Fig 3 Possible effects of increasing the amount of drug administered on plasma drug levels when drug elimination occurs by first order kinetics dose-dependent kinetics and zero order kinetics Amount of drug in the body is shown on the *ordinate* and time on the *abscissa* For curve *A* an equal amount of a drug (which is eliminated by first order kinetics) is being administered orally every six hours as a single dose *(at the arrows)* Plasma level gradually increases and a plateau level is reached when the amount of drug eliminated equals the amount administered For curve *B* the amount of the drug administered every six hours is increased but the t½ for elimination remains the same Plasma level now increases to a higher value before a plateau level is reached For curve *C* the amount of the drug administered every six hours is increased *further and at a critical plasma level the t½ for elimination* now becomes prolonged (so-called dose dependent elimination) A plateau level for the drug is not attained within the 72 hours shown on the graph instead the plasma level continues to rise For curve *D* the amount of drug administered every six hours is increased still further and now the metabolizing enzyme system becomes saturated Elimination now follows zero order kinetics and the plasma level rises precipitously The dashed line *E* shows the predicted plasma levels if there were no drug elimination (zero order kinetics at all dose levels)

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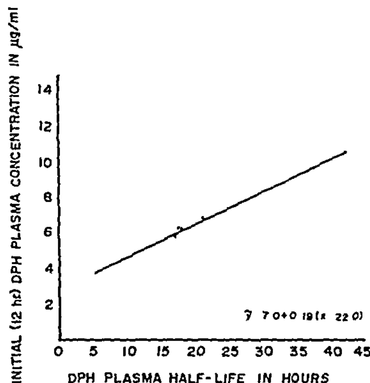


Fig 4 DPH plasma half life as a function of plasma concentration 12 hours after the last oral dose in human subjects Doses ranging from 100 mg to 1 000 mg were given daily for three days The plasma half life is increased as the plasma concentration of DPH increases (Reproduced from Arnold and Gerber The rate of decline of diphenylhydantoin in human plasma Clin Pharmacol Ther 11 122 1970 Reproduced by permission)

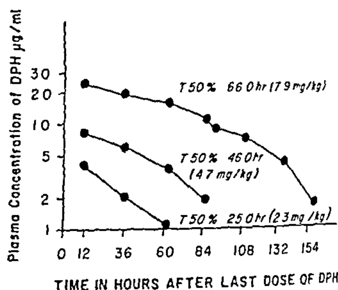


Fig 5 Rate of decline of DPH in the plasma of a single patient at three different plasma levels The lower curve demonstrates that after 2 3 mg /kg per day for three days the plasma concentration was 4 3 µg/ml The t½ determined after drug administration was stopped was 25 0 hours. In the middle curve after 4 7 mg /kg per day for three days the plasma concentration was 9 5 µg/ml and the t½ for elimination increased to 46 0 hours. The top curve shows that after administration of 7 9 mg /kg for three days plasma concentration of DPH was 25 µg/ml and the t½ for elimination was 66 0 hours. Thus the t½ for elimination is dose-dependent being longer at higher plasma concentrations. (Reproduced from Arnold and Gerber The rate of decline of diphenylhydantoin in human plasma Clin Pharmacol The 11 122 1970 Reproduced by permission)

plasma levels are high relatively small increments in the daily dose may result in a large increase in plasma levels in some patients that could cause toxicity

Factors influencing DPH plasma levels Any abnormalities in the process of absorption plasma protein binding or metabolism may result in large deviations in plasma DPH levels from the expected

Many factors may increase or decrease the rate of DPH metabolism Since the liver is the primary site of metabolism the state of liver function is important The mixed function oxidases responsible for DPH metabolism are located in the central area of the liver lobules and any damage to these areas can slow the rate of metabolism Patients on prolonged DPH therapy have developed signs of DPH intoxication after contracting infectious hepatitis[39] or after halothane anesthesia[40] associated with temporary impairment of liver function Impaired DPH metabolism has been observed in patients with liver cirrhosis [39] In these situations, abnormally high plasma levels of DPH may occur on standard dosage regimens However in most instances of liver disease clinical impairment of DPH metabolism is not evident perhaps because the sites of metabolism are not critically involved [25]

In rare individuals genetic factors may dictate an abnormal rate of DPH metabolism A small number of patients cannot metabolize more than 1 to 2 mg /Kg /day The daily output of HPPH in the urine of these patients is extraordinarily low During chronic DPH administration they accumulate unmetabolized drug in their plasma without reaching a plateau level[41] and intoxication readily occurs on standard therapeutic regimens

Liver metabolism of DPH also may be inhibited by other drugs including dicoumarol phenylbutazone disulfiram phenyramidol isoniazid methylphenidate chloramphenicol and phenothiazines [25] Such drugs apparently prevent the mixed function oxidase system from metaboliz

ing DPH DPH intoxication has occurred in patients receiving adequate maintenance therapy after one of the above agents was administered

Several factors also may result in accelerated DPH metabolism and abnormally low plasma levels in spite of standard dose regimens Kutt and associates[?] described patients who have abnormally rapid metabolism of DPH resulting in low DPH blood levels (1 to 2 μg/ml) with average daily doses The reasons for such rapid metabolism have not been elucidated Increased activity of the DPH metabolizing enzymes may be induced by other drugs such as phenobarbital[?] Several authors have reported that the chronic administration of phenobarbital to patients on maintenance DPH therapy resulted in a gradual decline in the DPH plasma levels and a reduction of the biological half life of DPH This does not occur in all patients and in some patients DPH levels are elevated after phenobarbital administration Although lowering of plasma DPH concentrations and accelerating its t½ for elimination by phenobarbital in man and experimental animals indicates enhanced DPH metabolism there is no direct demonstration of DPH metabolizing enzyme induction in man

Alterations in plasma protein binding of DPH may also significantly influence the plasma drug levels The measurements of plasma levels of DPH include both the drug which is bound to plasma protein (approximately 85 per cent of the drug in the plasma) and the unbound drug (approximately 15 per cent) At steady state the total amount in the plasma is only 6 to 7 per cent of the drug in the body[?] In patients with uremia or with hepatic disease plasma protein binding of DPH may be decreased possibly due to decreased plasma albumen concentration as well as a qualitative change in the plasma proteins[?] As a consequence of the decreased plasma binding more DPH may enter the tissue where it is bound to tissue proteins The total plasma concentrations of DPH will therefore be less than expected and tissue levels of drug may be higher As a result in uremic patients therapeutic and toxic effects may occur at lower than expected plasma DPH levels In addition plasma [K] may be elevated in uremia and this may potentiate a depressant effect of DPH on the electrical activity of cardiac tissues and cause toxicity

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Annotations

Single dose block-replace regimes in the treatment of hyperthyroidism

While the etiology of hyperthyroidism remains obscure rational therapy cannot be defined. The use of subtotal thyroidectomy is diminishing due to recognition of the high endocrine morbidity (hypothyroidism 25 per cent recurrent hyperthyroidism 14 per cent) in studies such as those of Becker and co workers in which 5 ??1 subjects were carefully followed up Accordingly surgery is being increasingly reserved for situations where compression features and su pi cion of malignancy are present Although radioiodine (I or I) is finding a progressively greater role in the younger thyrotoxic patient continued but admittedly unbased appre hension of possible carcinogenic and teratogenic effects has resulted in continuing usage of antithyroid drugs on a wide scale in many centers Furthermore destructive treatment is less than ideal in a disorder where spontaneous remission rates of up to 25 per cent have been suggested In order to lighten the burden of long term antithyroid drug treatment tradi tionally given in divided daily doses it was previously shown by Greer Meikoff and Studer[4] and Kammer and Srinivasan that single daily doses of propylthiouracil or methimazole were capable of controlling hyperthyroidism in a majority of hyperthyroid subjects over long periods

To further facilitate treatment a study was undertaken to identify a dose of carbimazole (C B) capable of subtotally blocking thyroid hormone biosynthesis in a single daily dose meanwhile maintaining euthyroidism with a standardized dose of triiodothyronine (T)

After preliminary assessment of dosage regimes C B 40 mg combined with T 60 to 80 µg were evaluated in 30 subjects (recently extended to a consecutive total of 40 subjects) Drugs were commenced in traditional divided daily dosages with a mean pretreatment free thyroxine index (F T I) (±S D) of 33 1 ± 12 1 units (assessed as the ratio between serum total thyroxine [T] and thyrobinding index) The F T I fell to 3 8 ± 0 6 units within three months Since the administered T is not measured in the assay systems and since all F T I values were in the hypothyroid range with the patients being clinically euthyroid it was inferred that block replace therapy was a sound concept Patients were then transferred to a single daily dosage of the above drugs in identical dosages and evaluated every three months over an 18-month period F T I remained at 3 7 ± 0 7 at three months and even showed a slight fall over a 1? month period to 3 3 ± 0 5 Subsequent acceptability already high was enhanced by formulation of a 20 mg C B tablet and a transfer to T 0 15 mg daily on which regime serum T and thyrotrophin (T S H) levels confirmed a euthyroid status in all eight subjects currently evaluated

The advantages of this regime are increased patient acceptability the lack of need for varying dosage in response to cl nical or biochemical assessment and the consequent ability to treat patients at a distance from clinical or biochemical facilities. The use of early uptake studies to define suppressability as a guide to postmedication relapse or remission is also facilitated by the continuous suppression" procedure

The invariability of response encountered up to the present time suggests that the assessment program for responsiveness to a single daily dosage using perchlorate discharge as suggested by Barnes and Bledsoe may be unnecessary with the dosages used in the present study and if treatment is initiated with divided daily dosage

The block replace principle has been extended to the use of ablative doses of I in patients in the older age groups with administration of T one month after radioiodine administration Monitoring of F T I allows verification of whether ablation has occurred. To the present time 16 out of 20 subjects in whom 1? to 15 mCi of I were given have been successful in achieving this aim and have been transferred to life long T replacement reinforced by a Medicalert bracelet system

The overall success of these approaches demands extended evaluation but at this stage they appear to provide significant advantages for patient welfare

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Diverticular disease and varicose veins

Diverticular disease is the commonest disease of the large intestine in Britain and North America It is estimated to be present in at least a third of the population over 40 years of age and two thirds of the population at 60 years Varicose veins are the commonest venous disorder affecting some 15 per cent of the adult population

In contrast diverticular disease is almost unknown and varicose veins are rare in developing countries

Burkitt has pointed out that varicose veins and diverticular disease have a very similar geographical distribution the incidence varying directly with the degree of economic development of the country

He has also stated that since all the effects of any cause tended to be associated with one another a recognized association between two or more diseases suggested an etiological factor common to both or all Consequently such diseases not only have a similar geographical distribution but tend to occur together in individual patients more frequently than would be expected from the prevalence of each in the community

In view of the demonstrated geographical relation between diverticular disease and varicose veins we decided to determine whether the two conditions tended to be associated in individual patients

A varicose vein was defined as dilated tortuous vein and five groups of patients were examined for the presence of varicose veins

Group I	One hundred patients randomly selected who attended as outpatients for non venous disorders
Group II	Eighty three patients with a normal barium enema
Group III	Sixty patients with diverticular disease demonstrated on barium enema
Group IV	Fifty patients all of whom had undergone surgery for diverticular disease
Group V	Three hundred thirty patients consisting of three age and sex matched controls for each patient in Groups III and IV

The prevalence of varicose veins in the five groups is given in Table I

Table I Prevalence of varicose veins

	Group	Total	Varicose veins
I	Randomly selected outpatients	100	16 (16%)
II	Normal barium enema	83	40 (48%)
III	Diverticular disease on barium enema	60	44 (73%)
IV	Diverticular disease at operation	50	37 (74%)
V	Matched controls for groups III and IV	330	110 (33%)

The greater prevalence in patients with diverticular disease than in the age and sex matched controls was statistically significant ($P < 0.001$)

The prevalence of varicose veins in the randomly selected outpatients correlates closely with the findings of others. The increased prevalence in patients with a normal barium enema suggests that the symptoms for which the investigation was requested may have been due to a prediverticular condition in some cases.

Of the 110 patients with diverticular disease (Groups III and IV) in 90 the condition was limited to the pelvic colon in 17 it involved the descending and pelvic colon and in three the entire colon was affected but there appeared to be no correlation between the severity of the diverticular disease and the extent of the varicose veins

Our findings support the hypothesis put forward by Cleave that diverticular disease and varicose veins are different manifestations of a common causal factor

Painter s work has led to wide acceptance that diverticular disease is caused by raised pressures in the lumen of the colon resulting from the fecal arrest consequent on a low residue diet—the characteristic diet of modern Western civilization

Cleave postulates that the relation between fecal arrest and varicose veins is due to pressure exerted by a loaded pelvic colon or a loaded prolapsed cecum on the iliac veins

Burkitt [4] fully supports Cleave in his incrimination of a low residue diet as the primary cause but suggests a different mechanism He believes that it is due to raised intra abdominal pressure resulting from straining at stool. This raised pressure which is known to be transmitted down the leg veins after the valves become incompetent appears to cause the initial valve failure Vena caval pressures of up to 300 to 400 mm Hg have been recorded with straining

These explanations are consistent with epidemiological and other evidence whereas conventionally accepted theories as to the primary cause of varicose veins such as heredity pregnancy constrictive clothing and man s lack of adaptation to the erect posture are untenable and quite inconsistent with epidemiological evidence

It is of interest that 35 per cent of our patients with diverticular disease had previously undergone appendectomy and 11 per cent had had cholecystectomy

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Myocardial infarction

Do we really know when an infarct is prevented? We do know when it is produced!

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Comparative yield of ECG leads in multistage stress testing

Exercise testing for detection of coronary artery disease is based chiefly on production of deviation of the S-T segment of the electrocardiogram (ECG) Selection of the ECG lead or combination of leads which detects this phenomenon with greatest accuracy is therefore of the highest order of importance the subject however has been curiously neglected Blackburn and Katigbak demonstrated early in the history of the method in a study of 100 patients that Lead V recorded alone would detect 89 per cent of available information in terms of S T deviation 11 per cent would be detected only if other leads were recorded (chiefly Leads II aV and V) Mason and co-workers in a study of 56 patients, found that 19 patients were positive in one lead only and that of these 19 patients seventeen were positive in leads other than Lead V (four in inferior leads two in Lead V_x four in V and seven in Lead V)

These findings have been substantially ignored by many subsequent investigators in the field who have confined their observations to a single bipolar lead with a positive electrode at the V position

Since a loss of 10 to 30 per cent in sensitivity must diminish the usefulness of stress testing significantly it seemed appropriate to analyze a large number of stress tests with the goal of determining definitively the most sensitive combination of leads for detection of S T deviation

Multi stage stress tests (4 197) were divided into two groups Group A, nine leads recorded (Leads I II III aV aV aV V_x V_x and V) In this group 411 tests were graded as positive (1 millimeter S T *depression* flat or downsloping for 0 08 second) In 59 tests (14 5 per cent) S T depression *was noted exclusively* in leads other than Lead V as follows 28 (8 5 per cent) S-T depression in *Leads II III and aV* 7 (1.9 per cent) S-T depression only in Lead V 7 (1 9 per cent) S T depression in Leads II III aV and V_x.

Group B *full conventional leads* recorded 947 studies 147 positive Thirty-eight (21 per cent) S T depression exclusively *in leads other than Lead V* Twenty three (12 84 per cent) S-T *depression only in Leads II III* and aV 3 (1 6 per cent) S-T depression in Leads II III aV_r and V 5 (2 79 per cent) S T *depression in Lead V only* 3 (1 67 per cent) S T depression in *Lead V only* 1 *(0 55 per cent) S T depression in Lead V only* 1 (0 55 per cent) S-T depression in Lead I 2 (1 1 per cent) *positive in Leads V* V and V only

This analysis of 590 positive stress tests revealed that failure to record leads other than Lead V will introduce a *negative* error of magnitude 15 to 20 per cent in stress testing in specific *terms of* detection of S T depression The well-documented percentage of false negative responses in patients with demonstrated coronary artery disease (about 24 per cent) may be in part a result of this procedural deficiency

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A knowledgment is made of National Institutes of Health support (Fund No 5-SO1 RR05067-05) for this study

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11 Detry J M R Exercise testing and training in coronary heart disease Rev Inst Hyg Mines (Hasselt) 27 5 1972

Letters to the Editor

First heart sound and mitral valve tension

To the Editor:

We disagree with two conclusions of Luisada and colleagues (AM HEART J 88 503 1974) that the first heart sound occurs *after* closure of the mitral valve and that the contribution of mitral valve *tension* to S1 is minimal

It is unfortunate that this eminent group of cardiologists and phonocardiographers published an article on "changing views" without adequately reviewing the only study which relates intracardiac S1 to transmitral flow and valve motion Had they considered our work more carefully they would have seen that their objections to our investigation are invalid They reject our study on two grounds (1) movement of the flow probe would cause "simulation of mitral flow" and (2) an absence of "a" waves in the LAP tracings as well as a reduced filling period in mitral flow tracings suggest a severely compromised left atrial function

Neither of these objections is valid (1) When the left ventricle contracts the descent of the mitral annulus produces a relative motion between the probe and the blood which would either appear to shorten the filling period or give an apparent backflow artifact If there is an error in timing as is claimed by Luisada and colleagues, it would tend to be in the direction which *substantiates* our findings regarding the temporal coincidence of S1 with cessation of flow and valve closure (2) "a" waves certainly were present in our LAP tracings (Figs. 1 2, 3 and 5) Although the high heart rate in anesthetized dogs reduces the filling period so that atrial augmentation is not always evident in the flow trace it can easily be seen in our Figures 2 to 5 But while we feel that left atrial function was *not* severely compromised this is not relevant Even if it were compromised our records indicate that flow continues across the mitral valve about 30 msec after A V pressure cross-over clearly as long as there is flow the valve must open

Luisada's group has long championed the application of physical principles to physiology Thus we fail to understand why they reject the existence of momentum in blood flowing across the mitral valve particularly when it has been accelerated by an atrial contraction Because of fluid momentum an adverse gradient is required to decelerate the inflow before the mitral valve can close This development of pressure takes time as Nolan and associates showed six years ago Although we were not the first to demonstrate this we were the first to demonstrate that cessation of flow coincided with closure of the mitral valve and the first large amplitude component of S1 It is clear to us that any discussion of the possible mechanisms of production of the first sound and its hemodynamic correlates must be consistent with these findings Participation of mitral valve closure in S1 can no longer be ruled out by the incorrect assumption that closure occurs at the moment of A V pressure cross over

We do agree with Luisada and colleagues that the entire cardiohemic system is set into vibration but we think that the evidence points to the major participation of the *tensed* mitral valve and its attachments. Briefly stated our thesis is that ventricular contraction or in the case of prolonged P R interval, atrial relaxation at the time of rapid diastolic pressure build up in the ventricle results in a reversal of the A V pressure gradient which decelerates mitral inflow The valve closes and tenses as the ventricular pressure rapidly rises At this point the vibrating system consists primarily of the mitral valve its elastic attachments and the mass of the blood and myocardium The system possesses both mass and elasticity and will vibrate under the action of an applied force The amplitude of the vibration depends on the magnitude of the force so that S1 will always occur after the pressure cross over (even when there is no blood to decelerate) since the pressure development takes time (as, for example after a prolonged diastasis with no atrial contraction) This explains why the mitral valve can coapt with premature reversal of the gradient and produce either a very soft S1 or none at all

Our latest study correlating the mitral valve echogram with phasic mitral flow substantiates our previous findings. In the normal dog (Figs. 2 and 3) there is a clear atrial augmentation of flow with an "a" wave in the echogram and an S1 at the time of valve closure A premature atrial contraction with prolonged P R interval (Fig 4) decelerated inflow and produced a small amount of regurgitation but the valve stayed open and S1 coincided with the subsequent closure of the valve following ventricular contraction In another sequence of spontaneous P R prolongation (Fig 9) where atrial relaxation caused a reversal of the pressure gradient and the valve moved toward coaptation and closure before ventricular systole S1 did not appear until rapid LV pressure development, and because the cusps were already in approximation S1 was softer Thus while closure is a necessary condition for the production of S1 it is not sufficient The valve must also be under tension

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Acronymic absurdity

To the Editor

The trend (T) of using (U) frequent (F) letter (L) abbreviations (A) for important repeated (R) words (W) in original (O) papers (P) in scientific (S) periodicals (P) has become (B) a significant impediment (I) to effective thought (TH) communication from writer (W) to reader (R) This T is B ing a disease (D) in the American Heart Journal (AHJ) The LA are F ly of the key W which express new (N) THs

The Ws need to be R to allow a learning (L_r) experience (EX) for the R_r Instead A s require F interruption of TH process (PR) to refer back to the O use of a W in the P The W thus loses (LO) control of the R s TH PR and the R LO continuity of the THT Time necessary to gain a N idea increases The LA of the W produces poor (PO) S literature and gives PO education and a frustrating EX to the R_r As editor of the AHJ you could help cure this D of AHJ and relieve the I in the continuing L_r of the R of S P by eliminating the U of LA s in the AHJ

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and Terdiman R A study of the dynamic relations between the mitral valve echogram and phasic mitral flow Circulation 51 104 1975

Reply

To the Editor

Our recent review on the mechanism of the heart sounds has raised considerable interest and of course some controversy This is good because only through a dispassionate examination of the facts can a final agreement be developed

Drs Yellin Laniado and Frater complain that our appraisal of their work was brief Nothing more could be done as their paper appeared during the publication of our review

Our comments are now the following

1 If a flow probe is sutured to the mitral ring a rise of this structure during the early part of systole would cause a simulation of flow through the mitral valve It is true that during the ejection phase the ring moves downwards However the opposite occurs during the isovolumic tension period an upward movement can be clearly seen in the old ultrasound tracings of Edler[1] and is revealed by a rise of pressure in the pressure tracings of the right and left atria as well as in the esophagocardiogram (Wiggers[2]) As no regurgitation into the left atrium occurs at that time and a bulging of the mitral valve is revealed by a high speed cineangiogram (MacCanon Bruce Lynch and Nickerson[3]) it is obvious that the mitral valve is already closed

Flow tracings through a catheter tip probe (Dresser and Benchimol[4]) may have a similar simulation of flow because the probe is anchored to a neck vessel and does not move while the ring moves

2 The statement that true closure of the valve occurred 40 msec after the crossing point of atrial and ventricular pressure would mean that completion of closure would not occur until the left ventricular pressure has reached levels of 30 to 50 mm Hg. This would obviously cause mitral regurgitation and delay aortic valve opening Should the latter not be delayed the isovolumic contraction period would be reduced to a mere 18 to 20 msec instead of the average 38 msec found in normal man by Luisada and Cortis[5] and longer periods by others in cardiac patients We know that no regurgitation occurs and we cannot visualize a flow of blood from a low pressure chamber (5 to 8 mm Hg) to a high pressure chamber (30 to 40 mm Hg) without having a power source behind it

3 The question of the momentum of a flow has been raised in regard to the semilunar valves and is generally accepted In the case of the semilunar valves the blood is flowing between each ventricle and the corresponding artery during a phase of similarly declining pressure in both Should the aorta have a powerful source of pressure causing the latter to rise in early diastole no momentum would occur

4 It has been thought in the past that the papillary muscles had an early contraction More recent studies (Cronin Armour and Randall[6]) have shown that in spite of early activation intraventricular pressure frequently rises considerably in advance of the development of increased tension in the papillary muscle Thus the mitral valve *tension* during most of the isovolumic contraction period would not be able to cause vibration of the chordae because they are lax

5 In regard to the findings of the echocardiographic method and in spite of some technical inaccuracies of the method *per se* (see our previous answer in this column) one can refer to the study of Ziady, Hardarson and Curiel[7] who have been able to record clear-cut B points that slightly *preceded* the first rapid vibration of the first sound and coincided with the onset of left ventricular pressure rise

6 Thus *closure* of the mitral valve is caused (with sinus rhythm) by relaxation of the left atrial musculature and eddies below the leaflets as already stated by Sarnoff Gilmore and Mitchell and basically accepted by Zaky Steinmetz and Feigenbaum Left ventricular contraction causes a *tensing* of the valve leaflets. This however can create sound vibrations only in proportion to motion of the structures and their mass (in the range of about 10 per cent of the energy of the first sound) as determined by MacCanon and colleagues.[3]

One more consideration should be made All clinical cardiologists have been taught that the first sound is caused by a mechanism different from the one outlined in our article Removal of the effects of this conditioning is difficult and painful as one of us (A.A L.) has experienced during 15 years of experimental studies that led him gradually to a new path Others will have to submit to the same process or else old errors will be perpetuated

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Prolact n 1974 By D F Horrobin St Laurent, Montreal, Quebec, Canada 1974 Eden Press 156 pages Price $15 00

Prolact n Physiology and Clinical Significance By David F Horrobin St Laurent Montreal, Quebec Canada 1973 Eden Press 240 pages Price $18 00

L Embolie Gazeuse du Systeme Carotidien Edited by G Arfel and R. Naquet Paris France 1974 Doin Editeurs 232 pages

Hypothermia in Biology and in Medicine By Vojin Popovic D Sc., and Pava Popovic D Sc., New York 1974 Grune & Stratton Inc 305 pages

Rehab litive Kardiologie By H Mellerowicz J Weidener and E. Jokl, Basel 1974 S Karger A G., 173 pages. Price $35 75

Book reviews

Symposium on Myocardial Metabolism An American Heart Association Monograph Number 41 Eugene Braunwald Heart Association New York 1974 215 pp

This symposium on myocardial metabolism briefly describes very well the state of knowledge of metabolism of heart muscle It is the heart muscle which is responsible for the pumping of blood Its energy and function depends upon the state of myocardial metabolism The metabolic problems discussed are fairly extensive The contributors are experts in their respective fields This publication should interest physiologists biochemists and those directly concerned with heart muscle energetics and metabolism The symposium clearly indicates the extensive gaps in knowledge of heart muscle metabolism in health and in disease

Vectorcardiography—Self Assessment By Edward K Chung M D Hagerstown Maryland 1974 Harper & Row Publishers 114 pp

Chung has gathered 100 fairly common electrocardiograms and vectorcardiograms for readers to study learn and to assess their knowledge of vectorcardiography The vectorcardiograms were all recorded by the Frank reference system of lead placement Many readers of course will have their reservations concerning the practicability of this method of lead placement in daily practice Regardless the recorded vectorcardiograms are sufficiently representative to be useful to those who employ other lead systems The Frank system tends to smooth out the vectorcardiographic complexes and thereby fails to reflect high frequency components of the vectorcardiogram The author rightly emphasized the importance and need to interpret the vectorcardiogram with the electrocardiogram The book provides a good review of clinical vectorcardiography and it is recommended for study This is a good book

Differential Diagnosis of the Electrocardiogram 2nd edition By Sidney R Arbeit Ira L. Rubin and Harry Gross Philadelphia 1975 F A Davis Company 218 pages Price $17 50

This is a training manual The subject of electrocardiography is presented in a simplified manner with the support of numerous diagrams and electrocardiograms Methods of analyzing electrocardiograms for arrhythmias and interpreting tracings from disturbances in wave form are discussed in a simple fashion and at times in an arbitrary manner found to be useful by the authors as well as others The reader must study and learn the electrophysiologic principles to understand why this simple approach to the interpretation of electrocardiograms actually works This point is well illustrated by Figures 2 and 3 However to understand electrocardiography an adequate knowledge of electrophysiology is essential The approach to teaching the reader to interpret electrocardiograms is good This book is recommended to all physicians who interpret tracings Beginners in particular will find the book most useful

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Editorial

Diabetes and the heart

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Cincinnati Ohio

Magnitude of the problem The estimated prevalence of known coronary artery (atherosclerotic) disease (CAD) in the United States is 3 870 000 with an annual mortality of 675 580 [1] The number with clinically silent CAD is not known Coronary artery disease has assumed epidemic proportions although recent observations suggest some decline in age adjusted death rates [2]

The estimated prevalence of diabetes mellitus in this country is nearly 5 000 000 [3] The annual reported mortality of about 38 000[3] is thought to be an underestimate and it has recently been suggested that as many as 300 000 diabetic patients die each year Diabetes has moved recently from eighth to the fifth leading cause of death in the United States [5]

Importance of coronary artery disease in diabetes Coronary artery disease accounts for more than half of the deaths in diabetic subjects (with onset after the age of 20) and is thus the most frequent and hazardous risk in the diabetic population Autopsy studies reveal an increased incidence (and severity) of CAD in the diabetic subject (45 to 70 per cent) when compared to the nondiabetic subject (8 to 30 per cent) [7]

Several features of CAD in the diabetic subject deserve special emphasis In the younger diabetic patient (age 20 to 40) clinically significant CAD is quite common particularly when the duration of diabetes is long [7] In the mature onset diabetic CAD tends to pursue an accelerated course and may in fact be the presenting clinical picture The premenopausal diabetic female has a prevalence of CAD equal to or even exceeding that of the diabetic male of comparable age Hypertension is more prevalent in the diabetic subject than in the nondiabetic population [8, 9] Coronary artery disease is twice as common in the diabetic hypertensive subject (as compared to the nondiabetic hypertensive subject) [9] The rarity of malignant hypertension in the patient with long standing diabetes and diabetic complications may be related to decreased renin activity

The prevalence importance and even the existence of small coronary artery disease in diabetes is unresolved [11, 13] A recent interesting report of myocardial biopsy in eight diabetic patients with heart failure or angina has revealed intimal arteriolar proliferation in all.[1]

Myocardial infarction in the diabetic subject Myocardial infarction bears an ominous prognosis in the diabetic subject Partamian and Bradley[15] found the early mortality for hospitalized diabetic patients with acute myocardial infarction to be 38 per cent for initial and 55 per cent for subsequent attacks These figures are to be contrasted with the overall inhospital mortality rate for myocardial infarction of about 25 to 35 per cent on the general medical service and 15 to 20 per cent in the coronary care unit

From th Divisi n of Cardiol gy Department f Medi in Uni rs ty f Cincin ti Coll g f Med cin Cincinnati.

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Reprint requests Cardi c Laboratory B-4 Univ rs ty of Ci cin ati Medical Cente 234 Goodman St Cincinnati, Ohio 45 29

Purdue Defibrillation Conference

The Biomedical Engineering Center of Purdue University will hold a conference in Lafayette Indiana from October 1 to 3 1975 covering the practical and clinical aspects of cardiac defibrillation The speakers have been selected based upon their positions as leaders in their respective fields. The topics to be discussed include clinical basic science and engineering aspects of electrical defibrillation as it pertains to the needs of physicians nurses emergency medical personnel hospital engineers equipment manufacturers and research scientists. The state-of the art of defibrillation techniques will be presented and examined critically and a major goal of this three-day conference will be to integrate all available technology for optimization of ventricular defibrillation The registration fee of $95 includes admission to the proceedings and two luncheons.

For further information please write Division of Conferences and Continuation Services, Stewart Center Purdue University West Lafayette Indiana 47907 Telephone (317) 749-2533.

lence (63 to 67 per cent) of preclinical (latent) diabetes (as demonstrated by an abnormal glucose tolerance test) in patients with angio graphically demonstrated significant premature CAD [49] This of course is a select population that has been studied by coronary arteriography If these prevalence figures of abnormal carbohy drate metabolism can be translated to all patients who die of CAD then it can be appreciated immediately that diabetes may contribute to a much larger proportion of deaths in this country than has been reported [3]

Hyperlipoproteinemia and coronary artery dis ease Elevated serum lipid levels are common in patients with CAD [50 51] A recent study of 500 survivors of acute myocardial infarction has revealed that 31 per cent had hyperlipidemia with men under 40 and women under 50 having a frequency of 60 per cent [2] Triglyceride elevation (with or without hypercholesterolemia) was three times as common as isolated hypercholestero lemia Overt diabetes occurred in 13 per cent of all survivors with a higher frequency (19 per cent) in the group with hypertriglyceridemia [2]

Coronary arteriographic studies have revealed a high prevalence of hyperlipoproteinemia (54 to 74 per cent) in patients with documented CAD with an especially high frequency (80 per cent) in patients under age 50 The lipopro tein abnormalities were about equally divided between type II and type IV [8]

Obesity Acquired obesity is associated with an increased prevalence of abnormal carbohydrate metabolism (both overt mature onset diabetes and patients displaying only an abnormal glu cose tolerance test) [3] increased insulin pro duction (and resistance) [3 5 6] hypertriglycer idemia [6 5 5] and hypertension [1] Obesity alone however is an equivocal risk factor in CAD

Weight reduction is usually associated with an improvement in carbohydrate tolerance [3] more normal insulin production [8 3 53] decline in elevated triglycerides [5 56] and presumably through reduction in these associated risk factors a lessened risk of premature CAD

Insulin In the severe juvenile type diabetic subject there is an absolute or profound lack of insulin production [5] Without exogenous insu lin replacement there is marked hyperglycemia (due to impaired transport of glucose across cell membranes and to gluconeogenesis) lipolysis with increase in circulating free fatty acids (FFA) [50 3] (secondary to lack of insulin inhibi tion of hormone sensitive lipase) hypertriglycer idemia and chylomicronemia (secondary to low levels of insulin dependent lipoprotein li pase [33 59 60 6] and increased hepatic pro duction of pre β lipoprotein from FFA) and keto genesis [58 62] As previously noted with insulin therapy there may be a changing pattern of hyperlipoproteinemia [3]

Occasionally gross hyperlipemia (chylomicron emia) a form of acquired type I may occur in nonketotic long standing inadequately treated juvenile diabetic subjects [3 32 33] It has been suggested that there is enough insulin available to prevent uncontrolled lipolysis and ketogenesis (by inhibition of hormone sensitive lipase) but not enough to maintain adequate levels of lipo protein lipase (which is necessary for removal of the circulating triglycerides) [9]

Depending on the degree of control in juvenile diabetes there may be wide fluctuations in blood sugar and lipid levels What effect this may have in the production of atherosclerosis is at present largely a matter of speculation

In the mature onset diabetic subject (both overt and latent) serum levels of immunoreactive insulin (IRI) have been variously reported as low normal or high [41 57] It is generally accepted that in these patients there is both a delay in the initial insulin response to a glucose load and a prolonged secondary response [5 5 56] When total IRI secre tion is measured it has often been found to be absolutely elevated (although relatively de creased when compared to normal subjects for the degree of hyperglycemia) [5 5 5]

The precise cause of increased insulin secretion in carbohydrate intolerance is debatable [3] It has been proposed that there is some form of insulin resistance (or diminished responsiveness) in the peripheral tissues (especially muscle but less evident in adipose tissue) which interferes with glucose transport across the cell mem brane [3 5 6] The resultant hyperglycemia serves as an additional stimulus to the β cells of the pancreas to increase insulin production [9 5 5] This insulin resistance and resultant hyperinsu linism has been found especially in patients with acquired obesity [52 53]

A number of investigators have documented the frequent occurrence of hyperinsulinism in mild diabetes [34 5 2 5] obesity [4 5 55] hypertri

(CCU)[16,17] Comparative CCU mortality figures for a large series of diabetic and of nondiabetic patients with acute infarction are not available at this time

The five year survival rate in diabetic subjects is even more alarming being 38 per cent (62 per cent mortality) for those patients with single episodes and only 25 per cent (75 per cent mortality) for those patients with subsequent attacks[1]

A high incidence of shock (26 per cent) and congestive heart failure (67 per cent) has been reported in the diabetic subject with acute infarction[1] Another unusual feature is the high rate of painless infarction in the diabetic subject (24 to 42 per cent)[1, 19, 20]

Interrelation between hyperglycemia hyperlipoproteinemia and coronary artery disease There is a voluminous amount of literature which has appeared during the past few years attempting to relate hyperglycemia abnormal insulin response, hyperlipoproteinemia and obesity with premature CAD Many of the studies have yielded conflicting and confusing results and conclusions but a pattern appears to be emerging The following observations are a synthesis of many proposed mechanisms and certainly must not be construed as the final (or even necessarily the correct) interpretation of these various studies Continuing new investigations may drastically change our concepts as to the basic mechanisms responsible for these apparent relationships

Hyperlipoproteinemia in diabetes (abnormal carbohydrate metabolism) Hypercholesterolemia (increase in β lipoprotein), a well recognized risk factor in premature CAD[1,24] occurs in approximately 8 to 32 per cent of the patients with abnormal carbohydrate metabolism (both overt and latent diabetes)[7, 25]

Hypertriglyceridema (increase in pre β lipoproteins), now also recognized as an important risk factor in premature CAD,[26 2] has been found to occur in about one third of the patients with abnormal carbohydrate metabolism[10] Triglyceride levels have been shown to be higher in diabetic subjects with CAD (and other large vessel disease) than in either diabetic subjects without large vessel disease or in control patients without diabetes or CAD[8, 21, 9, 31] In a group of diabetic subjects aged 30 to 59 Santen Willis and Fajans[3] found elevated triglycerides in 50 per cent of those with clinically significant atherosclerosis but in only 15 per cent of those without atherosclerosis

Hypercholesterolemia and/or hypertriglyceridemia have been found to occur in 62 per cent of the patients with diabetes and atherosclerosis but in only about 27 per cent of the diabetic subjects without atherosclerosis[23] Acquired type I hyperlipoproteinemia may occur occasionally as a transient complication in the insulin dependent diabetic subject[3, 33]

The presently unanswered question is whether hyperlipoproteinemia is a result of diabetes, a causative factor in diabetes (unlikely),[34] simply a commonly associated condition, or whether both are a result of (or are associated with) some other metabolic defect

Fredrickson[35] has observed that a spectrum of hyperlipoprotein abnormalities may occur in severe ketoacidosis progressing from type V, type III, type IV and type II (often in that order) as control is regained with insulin treatment In the well controlled juvenile diabetic subject, the lipoprotein pattern may be normal[35]

Hyperglycemia in hyperlipoproteinemia Impaired glucose tolerance is common in patients with hypertriglyceridemia[34, 36, 37] Carbohydrate intolerance has been evaluated in a group (107) of patients with familial hyperlipoproteinemia[38] The prevalence was found to be 33 per cent in II 39 per cent in III 52 per cent in IV, and 77 per cent in V[38] The incidence of overt diabetes was low

Most individuals will demonstrate some increase in plasma triglycerides when given a high carbohydrate diet[39] This is due to increases in hepatic triglyceride secretion rates[39, 40] Some workers have found high carbohydrate diets to increase triglyceride blood levels up to one and one half to two times fasting levels in normal individuals[30, 41] Most type II and about one half of type IV patients with hyperlipoproteinemia do not have abnormal carbohydrate induction while most patients with type III have exaggerated carbohydrate induced triglyceride elevations[34, 42]

Hyperglycemia and coronary artery disease Hyperglycemia is well recognized as a risk factor in premature CAD[43, 44] There is a high prevalence (42 to 53 per cent) of clinically significant CAD in overt diabetes[18, 45, 47]

Perhaps even more fascinating and startling has been the demonstration of the high preva

is of interest that many of these patients have been found to have high levels of IRI (hyperinsulinism)[83]

Follow up studies have revealed that the glucose intolerance is usually of short duration (a few days to a few weeks) although a substantial number (32 per cent) of these patients have displayed a persistent pattern of glucose intolerance even after a year or more[77 81] while some 14 per cent have been found to develop clinical diabetes[8]

There are probably several explanations for this postinfarction carbohydrate intolerance The early display (as already described) is probably related to the acute stress[5] It has also been found that those patients with complications (shock congestive heart failure) display a more severe carbohydrate intolerance[55] The persisting glucose abnormalities in some patients may be related to the already described high prevalence of carbohydrate intolerance in coronary artery disease and finally in some to the unmasking of latent or overt diabetes[55 81 82]

Overview and outlook An enormous experience both clinical and experimental has accumulated during the past several years about the broad topics of diabetes hyperlipoproteinemia and premature CAD This editorial has attempted to place some of these advances in perspective and at the same time to speculate about their complex interrelationships As more knowledge (especially at the biochemical and molecular level) is gained perhaps some inroads can be made against the devastating vascular complications that these metabolic abnormalities produce

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glyceridemia,[8, 1, 41, 51, 64] and CAD[37, 50, 56, 65] It has been demonstrated that hyperinsulinism, in association with hyperglycemia promotes lipogenesis by increasing free fatty acid biosynthesis and esterification to triglycerides and inhibits the lipolytic activity of hormone sensitive lipase on stored triglyceride in adipose tissue with resulting obesity[38, 39, 41, 66] Insulin has also been clearly shown to promote free fatty acid biosynthesis and esterification to triglycerides in the liver[8, 39, 50, 67] The hepatic hormone sensitive lipase is also inhibited by insulin (through the mechanism of lowering hepatic cyclic AMP) resulting in a larger triglyceride pool in the liver with subsequent increased production and secretion of pre β lipoproteins (endogenous hypertriglyceridemia)[39, 67] The increased circulating triglycerides in turn are hydrolyzed to free fatty acids by the insulin stimulated lipoprotein lipase tending to perpetuate the cycle

The circulating pre β lipoproteins (VLDL) are thought to be degraded to β lipoproteins (LDL) which are high in cholesterol[68] This mechanism plus increased hepatic cholesterol synthesis from acetyl coenzyme A can be invoked to explain the occurrence of some cases of hypercholesterolemia in diabetes

Combined metabolic abnormalities in premature coronary artery disease The combination of hyperglycemia hyperlipoproteinemia and/or hyperinsulinism has been found in a remarkably large number of patients with premature CAD One or more of these abnormalities have been found in from 90 to 96 per cent of the patients with either clinically or angiographically documented CAD[48, 49, 50, 58, 69]

Remaining to be explained is the association of hyperinsulinism and premature CAD[56] The increased production and elevated blood levels of triglycerides and/or cholesterol (carried as pre β and β lipoproteins) which may be related to hyperinsulinism may contribute in some manner to the atherosclerotic process[51, 56]

Pathogenesis of coronary atherosclerosis Current concepts of the pathogenesis of atherosclerosis favor the lipid infiltration theory as best explaining the early development of atherosclerosis (while the thrombogenetic theory is important in the later prognosis of the lesion[70, 71]) Abnormal plasma elevation of β lipoprotein and pre β lipoprotein appear to be key factors in initiating the atherosclerotic process These lipoproteins continuously penetrate the endothelium and internal elastic membrane and accumulate in the smooth muscle cells[1]

A recent interesting hypothesis to explain the role of both triglycerides and cholesterol in atherogenesis has been formulated by Zilversmit He suggests that pre β lipoproteins are probably too large to penetrate the arterial intima while the smaller β lipoproteins readily infiltrate the intima[72] Lipoprotein lipase present in vascular endothelium produces lipolysis of triglyceride rich pre β lipoproteins and chylomicrons with the formation of cholesterol rich β lipoproteins Such surface lipolysis in large arteries could result in high local concentration of cholesterol rich lipoprotein (and potentially injurious free fatty acids) with enhanced cholesterol uptake by the arterial intima[72] Insulin is known to closely regulate lipoprotein lipase[5] and it is easy to conceive how hyperinsulinism in the mature onset diabetic subject could enhance local endothelial lipolysis in large arteries (including the coronary arteries) with accelerated atherosclerosis If this concept is correct then a high concentration of serum β lipoprotein is not the cause of atherosclerosis but the result of the enzymatic reaction that produces lipid deposits in the arterial intima[1]

Other factors to be considered in the occurrence of premature atherosclerosis (and its complications) in diabetic patients are the possible contribution of the sorbitol (polyol) pathway[73] which has been demonstrated in the aorta (in vitro),[1, 5] insulin enhanced lipid synthesis in the arterial wall[50, 56, 76] the enhanced platelet adhesiveness (particularly in premenopausal diabetic women),[77] and the recent demonstration that alcohol significantly increases plasma triglycerides in those patients with pre existing type IV hyperlipoproteinemia (which is common in diabetic subjects)[78, 79]

Carbohydrate intolerance in acute myocardial infarction It has been demonstrated that an astoundingly high number (65 to 100 per cent) of patients with acute myocardial infarction will exhibit carbohydrate intolerance[80, 82] This has been attributed by some to the stress of the acute episode with catecholamine release enhanced lipolysis with elevation of free fatty acids and consequent blunting of insulin activity[53, 63, 8] It

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Table I QRS loop rotation

Interrelationship of great arteries	*Frontal QRS loop*		*Horizontal QRS loop*		*No of patients*	*Row*
	Clockwise	*Counter clockwise*	*Clockwise*	*Counter clockwise*		
Dextrotransposition						
Type A common ventricle	5	2	1	6	7	1
Type C common ventricle	7	6	10	3	13	2
Total common ventricle	12	8	11	9	20	3
Large ventricular septal defect two ventricles	13	9	3	19	22	4
Levotransposition						
Type A common ventricle	18	2	9	11	20	5
Type C common ventricle	4	2	2	4	6	6
Total common ventricle	22	4	11	15	26	7
Large ventricular septal defect two ventricles	10	4	2	12	14	8
Normal						
Type A common ventricle	0	2	1	1	2	9
Type C common ventricle	[illegible]	1	3	0	3	10
Total common ventricle	2	3	4	1	5	11

Statistically significant differences ($P < 0.05$) in horizontal loop rotation between rows 1 and 2 between rows 3 and 4 between the sum of rows 1 plus 5 plus 9 and row 2 plus 6 plus 10 and between the sum of rows 3 plus 7 and rows 4 plus 8

Table II Ratio of voltage amplitudes of spatial initial forces to maximal spatial QRS vector

Ventricular anatomy	*No*	*Mean*	*Range*
Common ventricle	51	0 12	0 01 0 ?6
Large ventricular septal defect	36	0 20	0 01 0 46

Statistically different ($P < 0.05$)

position with an l loop) when the aorta arose to the left and anterior to the pulmonary artery [5]

All 51 patients with common ventricle and all patients with levo or dextrotransposition of the great arteries and ventricular septal defect had undergone cardiac catheterization and large film biplane angiocardiography Among 29 patients with type A common ventricle two had normally related great arteries seven had dextrotransposition of the great arteries and 20 had levotransposition Of 22 patients with type C common ventricle three had normally related great vessels 13 had dextrotransposition and six had levotransposition of the great arteries In patients with type A common ventricle the subaortic outflow chamber was usually situated to the left of the common ventricular chamber in the presence of levotransposition of the great arteries and anterior and to the right of the common chamber in the presence of dextrotransposition of the great arteries Of seven patients in whom a common atrioventricular valve opened into the ventricular chamber four had type A common ventricle with levotransposition of the great arteries and three had type C common ventricle (one with dextro transposition of the great arteries one with levotransposition of the great arteries and one with normally related great vessels)

Results

Intergroup comparisons between common ventricle and large ventricular septal defect (Tables I and II and Fig 1) In the frontal plane there was no significant difference in QRS loop rotation or directions of initial maximal mean and terminal forces between patients with common ventricle and those with ventricular septal defect Most of the patients in the two groups had predominant forces directed superiorly and to the right when frontal loop rotation was counterclockwise and directed inferiorly or superiorly and to the right when loop inscription was clockwise In all patients of each group the direction of mean forces was similar to the direction of maximal forces Initial forces were directed predominantly to the left in patients with both counterclockwise and clockwise frontal plane loops Regardless of loop rotation, terminal

Clinical communications

Frank vectorcardiogram in common ventricle Correlation with anatomic findings

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The Frank vectorcardiogram in common ventricle may be influenced by the anatomic relationship of the great arteries or by details of ventricular anatomy such as absence or presence of the sinus portion of the ventricles or the morphology of the rudimentary ventricular septum or of the atrioventricular valves

To determine the influence of various anatomic features of common ventricle on the Frank vectorcardiogram, we compared the vectorcardiograms of patients who had common ventricle of types A and C with the vectorcardiograms of patients who had large ventricular septal defect and either levo or dextrotransposition of the great arteries Gessner and co workers[1] have shown that patients with type A common ventricle and levotransposition of the great arteries can be differentiated from patients with ventricular septal defect

Material and methods

All Frank vectorcardiograms were obtained online with the Mayo Clinic computerized system described previously[2] In our institution, the precordial electrodes of the Frank system are placed along the fifth intercostal space with the patient in the recumbent position The output matrix of this system lists the direction and magnitude of the mean vectors over each 10 ms segment of the QRS vector loop in all three planes The maximal QRS vector in each plane represents the direction and magnitude of the maximal spatial vector projected onto this plane Magnitude and direction of the mean QRS vector in each plane are calculated from the average of all mean 10 ms vectors in this plane Initial forces in each plane are defined as the average magnitude and direction of the first three mean 10 ms vectors (initial 30 ms), and terminal forces represent the average magnitude and direction of the last four mean 10 ms vectors (terminal 40 ms) in each plane In this study, the magnitude and direction of the maximal QRS vector the mean QRS vector and the initial forces and the terminal forces in the frontal and horizontal planes as well as the rotation of the frontal and horizontal vector loops were analyzed Frank vectorcardiograms of 51 patients with common ventricle who were 3 weeks to 30 years old were compared with the Frank vectorcardiograms of 22 patients (ages 1 to 15 years) who had dextrotransposition of the great arteries and ventricular septal defect and with the Frank vectorcardiograms of 14 patients (ages 17 months to 28 years) who had levotransposition of the great arteries and large ventricular septal defect

Common ventricle was classified according to the ventricular anatomy[3, 4] In type A common ventricle (double inlet left ventricle)[1] there is a common left ventricular chamber into which both atrioventricular valves open and a small outflow chamber In type C common ventricle there is no outflow chamber The relationship of the great arteries was categorized as dextrotransposition (transposition with a d loop)[3, 4] when the aorta arose anteriorly and to the right of the pulmonary artery and as levotransposition (transposition with ventricular inversion or trans

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forces were directed to the right in most patients

Patients with common ventricle were more likely to have a clockwise horizontal loop than were those with two ventricles While most patients with ventricular septal defect and levo or dextrotransposition had counterclockwise horizontal loops (87 and 84 per cent of patients respectively) 26 of the 51 patients with common ventricle had clockwise horizontal loops There was no significant difference in directions of initial maximal mean and terminal forces in the horizontal plane between patients with common ventricle and patients with large ventricular septal defect

The ratio of the voltage amplitude of the spatial initial mean 30 ms vector to the maximal spatial QRS vector demonstrated that the initial forces were significantly smaller ($P < 0.05$) in patients with common ventricle than in patients with ventricular septal defect (Table II)

Intragroup comparisons within common ventricle (Table I Fig 1) Twenty two of the 26 patients with common ventricle and levotransposition of the great arteries had clockwise frontal QRS loops Horizontal rotation was clockwise in 11 patients and counterclockwise in 15

In the 20 patients with dextrotransposition of the great arteries 12 had clockwise and eight had counterclockwise frontal QRS loops In the presence of counterclockwise QRS loops the maximal QRS vector was usually directed to the right In the horizontal plane loop rotation was clockwise in 11 patients and counterclockwise in nine patients There was a significant difference ($P < 0.05$) in the horizontal loop rotation between patients with type C and those with type A common ventricle The rotation was counterclockwise in 18 of 29 patients (62 per cent) with type A common ventricle and counterclockwise in seven of 22 patients (32 per cent) with type C common ventricle There was no significant difference in the ratio of voltage amplitude of the spatial initial mean 30 ms vector to the maximal spatial QRS vector between patients with type C common ventricle and those with type A common ventricle Among the 51 patients with common ventricle only five had maximal spatial voltages that were not above normal when compared to the ninety fifth percentile of this variable obtained in 550 age matched normal control children[4] The mean voltage amplitude of the maximal spatial QRS vector in the 24 patients with common ventricle and pulmonary stenosis was 2.4 mV, whereas it was 3.2 mV in the 27 patients with common ventricle without pulmonary stenosis Although there was a statistically significant difference in mean values ($P < 0.01$) it was not possible to determine from the size of the maximal spatial QRS vector in an individual patient whether there was pulmonary stenosis

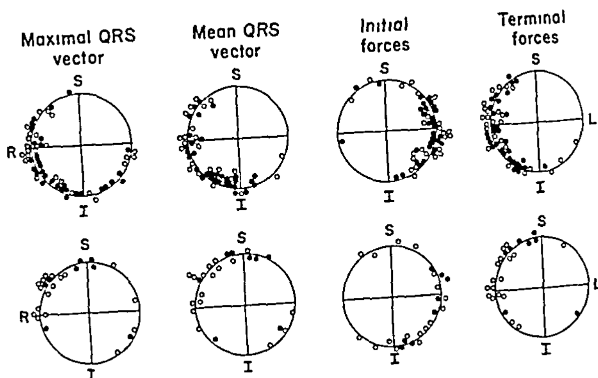
Discussion

Intergroup comparisons between common ventricle and large ventricular septal defect Neither our study nor previous reports[1,4,8] have been able to elucidate differences in initial terminal or mean forces in the frontal or horizontal plane to identify individual patients with common ventricle (Fig 1)

Only three of 22 patients (14 per cent) with large ventricular septal defect and dextrotransposition of the great arteries had clockwise horizontal loops with anteriorly and rightward directed maximal QRS vectors These features were encountered in 11 of 20 patients (55 per cent) with common ventricle and dextrotransposition of the great arteries In levotransposition of the great arteries horizontal vector loops were clockwise in 14 per cent of the patients with large ventricular septal defect and in 42 per cent of the patients with common ventricle Although the difference in horizontal rotation between patients with large ventricular septal defect and those with common ventricle was statistically significant the degree of overlap between the two groups is sufficiently great that this criterion is of limited usefulness in establishing the diagnosis of common ventricle in any individual patient

The Frank vectorcardiogram in patients with common ventricle showed a smaller mean initial spatial force than that in patients with the same anatomic arrangement of the great arteries and large ventricular septal defect Although the difference between mean values was statistically significant the findings were not specific enough to differentiate the two groups Small early forces in patients with common ventricle may be related to absence of or to small septal muscle mass and contrast with augmented early forces in patients with ventricular septal defect and levo- or dextrotransposition of the great arteries where the septum is usually hypertrophied[9]

Intragroup comparisons within common ven



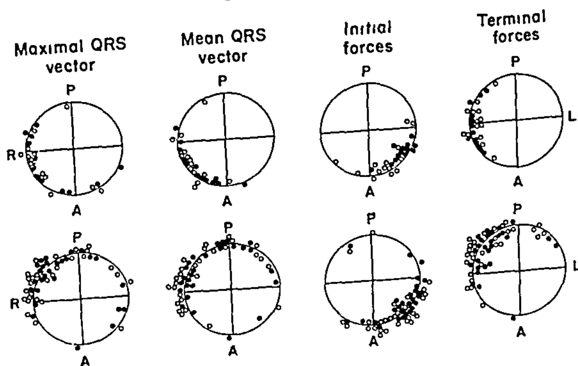


Fig 1 Direction of maximal mean initial and terminal forces in patients with common ventricle (within circle) and in patients with large ventricular septal defect (outside of circle) Open circles dextrotransposition of great arteries solid circles levotransposition of great arteries Top frontal plane bottom horizontal plane

Sinus node re-entrant tachycardia in man

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The mechanism proposed to explain atrial tachycardias include re entry and enhanced automaticity Re entry within the A V node is a common cause of paroxysmal supraventricular tachycardias while enhanced automaticity has been proposed as the mechanism for so called atrial ectopic tachycardias [4]

The results of experimental studies in isolated rabbit atrial tissue,[5] the intact dog heart [6 8] and man[9] have suggested that the region of the sinus node can also be the site of re entry In each of these studies a single closely coupled atrial premature depolarization (APD) was followed by an early atrial response which was considered to be an atrial echo beat due to re entry within the region of the sinus node In the intact dog heart and in man single atrial echo beats were observed to be the most common manifestation of sinus node re entry (SNR) Occasionally a single APD resulted in a post extrasystolic acceleration of the atrial rate for several cardiac cycles This latter finding provided evidence in support of previous proposals that sinus node re entry could be a mechanism for atrial tachycardias in man

This report deals with six clinical cases of atrial tachycardias having certain characteristics similar to those of A V nodal re entrant tachycardias These include (1) initiation and termination of tachycardias by properly timed APD s introduced within a relatively narrow range of coupling intervals (echo zones) (2) initiation by continuous atrial capture at relatively rapid atrial rates and (3) termination by maneuvers which increase vagal tone However re entry in these cases seemed to occur within the general vicinity of the sinus node since the atrial activation sequence recorded during the tachycardia was similar to that recorded during sinus rhythm These electrophysiologic characteristics of these arrhythmias the criteria for sinus node re entry, and the distinctions between sinus node and A V nodal re entry will be discussed

Materials and methods

Right heart catheterization was performed in six patients in the postabsorptive nonsedated state All patients were advised of the nature of the study and a signed consent was obtained Pertinent clinical data are given in Table I No patients were receiving cardioactive drugs at the time of the tudy

Using local anesthesia a quadripolar electrode catheter was percutaneously inserted into an antecubital vein and fluoroscopically positioned in the high right atrium Four patients in addition had quadripolar electrode catheters positioned within the coronary sinus The two distal electrodes were used for stimulation and the two proximal electrodes for recording atrial electrical activity from the respective sites In three pa

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Reprint requests Dr Anthony N Dam to C rd pulm nary Labo a toy Un ted States Publ c Health Hosp tal Stat n I la d N Y 10304

tricle Our study confirmed previous reports[1,4,8] in which most patients with common ventricle and levotransposition of the great arteries had clockwise frontal QRS loops Patients with dextrotransposition of the great arteries were more likely to have a counterclockwise frontal QRS loop Eleven of 29 patients (38 per cent) with type A common ventricle and 15 of 22 patients (68 per cent) with type C common ventricle had clockwise horizontal loops Gessner and co workers[1] speculated that clockwise horizontal QRS loops in common ventricle may be related to an anomalous course of the conduction system Anderson and co workers[10] have demonstrated an unusual position of the A V node in common ventricle type A

Van Praagh and co workers[7] noted that six of eight patients with common ventricle and one common atrioventricular valve had counterclockwise frontal QRS loop suggestive of an endocardial cushion defect In our study only two of seven patients in whom a common atrioventricular valve was demonstrated at angiocardiography had counterclockwise superiorly oriented frontal QRS loops with initial forces inferiorly and to the right (characteristic of an endocardial cushion defect) This suggests that, in common ventricle the pathogenesis of a common atrioventricular valve is probably different from that in endocardial cushion defect[11]

Summary

The influence on the Frank vectorcardiogram of anatomic features in common ventricle was analyzed by comparison of Frank vectorcardiograms in 51 patients who had common ventricle with those of 36 patients who had large ventricular septal defect 14 of whom had levotransposition of the great arteries and 22 of whom had dextrotransposition Frank vector loops in common ventricle differed from those in ventricular septal defect by the frequent occurrence of clockwise horizontal rotation, most common in patients with type C common ventricle (no outflow chamber) There was a statistically significant difference in the amplitude of early forces between patients with common ventricle and those with large ventricular septal defect The degree of overlap of vectorcardiographic features between the two groups is sufficiently great that the vectorcardiogram has limited usefulness in establishing the diagnosis of common ventricle in any individual patient

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Table II Electrophysiologic data

	Patients					
	RM	*WN*	*BC*	*JG*	*MB*	*MH*
Sinus rhythm						
CL	700 ± 15	560 ± 30	740	654 ± 60	770 ± 30	800 ± 50
AH	110	115	100	105	95	90
HV	60	55	45	45	45	45
Initiation of tachycardia						
A APD in HRA						
a) A A intervals during sinus rhythm	470 250	–	–	–	330	3[illegible]0 300(S S)
b) A A intervals during atrial paced cycles	–	350-280(550) 360-2[illegible]0(500)	390 320(700) 460 290 (600) 390-290(5[illegible]0)	280-2[illegible]0(600) 280-[illegible]45(500)	290-25[illegible](700) 330-300 (500)	305-260(700)
B APD in CS						
a) A A intervals during sinus rhythm	420-280	–	–	–	–	–
b) A A intervals during CS paced cycles	–	300-270 (500)	370-[illegible]60 ([illegible]00) 400-[illegible]60 (600) 3[illegible]0 300 (550)	410-280 (550)	–	–
C Atrial pacing	< 470	440 325	460-428	350	–	–
D Ventricular pacing	–	–	–	300	–	–
Duration of tachycardia	Sustained	17 beats	7 beats	Sustained	10 beats	21 beats
Cycle length of tachycardia	430	405	410	3[illegible]0	50[illegible]	6[illegible]5
Termination	Spontaneous A pace CSP Valsalva APD s	Spontaneous	Spontaneous APD s	Spontaneous APD s CSP Atrial capture from V pace	Spontaneous	Spontaneous
A V conduction during tachycardia	1 1 AVN Wenckebach	1 1	1 1	1 1 AVN Wenckebach	1 1	1 1

All numbers are in milliseconds.
Cycle length of basic drive is indicated in parentheses

gram recordings Records were subsequently played back and recorded at paper speeds of 150 to 200 mm per second

Definition of terms A the atrial electrogram of either a sinus or basic drive beat A_2 the atrial electrogram of the induced atrial premature depolarization (APD) $A_3A_4A_5$ etc the atrial electrograms of subsequent atrial beats A_1A_1 interval the atrial cycle length immediately preceding A_2 A_1A_2 interval the coupling interval of an APD $A_2A_3A_4A_5$ etc the intervals between corresponding atrial depolarizations Sinus node escape time the interval from the last paced atrial beat to the first spontaneous sinus beat or the interval from the last beat of a tachycardia to the first spontaneous sinus beat High to low activa

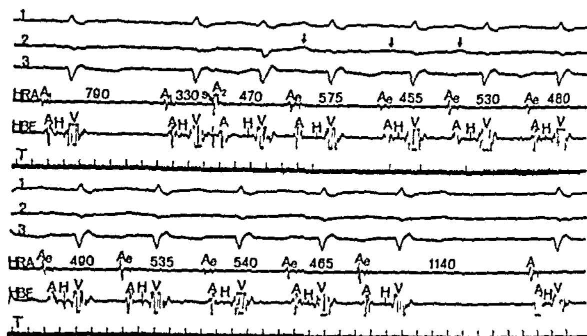


Fig 1 Premature atrial stimulation from the high right atrium during sinus rhythm resulting in a sinus node re entrant tachycardia Sinus cycle length (A_1A_1) is 790 msec A_2 is introduced in the high right atrium at a coupling interval of 330 msec and is followed by a tachycardia with an average cycle length of 502 msec Atrial activation recorded in the high right atrium precedes low atrial activity as recorded in the His bundle electrogram Arrows in Lead 2 indicate upright P waves The tachycardia terminates spontaneously after nine consecutive beats with a sinus escape time of 1 140 msec The illustration shows from top to bottom standard electrocardiographic Leads 1 2 and 3 high right atrial electrogram (HRA) His bundle electrogram (HBE) and time lines (T) at intervals of 10 and 100 msec A atrial deflection H His bundle deflection V ventricular deflection S stimulus artifact and Ae atrial echo beat This sequence and these abbreviations are used also in the subsequent figures

Table I Clinical data

Patient	*Age*	*Sex*	*Diagnosis*	*ECG*	*Chief complaint*
JG	50	F	Normal	Normal	Palpitations
MB	52	M	Essential hypertension	RBBB left axis deviation normal Pr	Vague dizziness
MH	63	M	Arteriosclerotic heart disease	Normal ST and T wave changes	Palpitations
BC	57	M	Normal	Left axis deviation ventricular premature beats	Asymptomatic
WN	65	M	Chronic obstructive pulmo nary disease	Left ventricular hypertrophy supra ventricular tachycardia	Episodic dyspnea
RM	59	M	Arteriosclerotic heart disease	Supraventricular tachycardia ST T abnormalities	Palpitations

tients, a bipolar electrode catheter was positioned in the right ventricular apex for ventricular pacing A tripolar electrode catheter was posi tioned in the region of the tricuspid valve to record a His bundle electrogram as previously described [12]

Incremental pacing of the high right atrium to the point of A V block was performed using a programmed digital stimulator which delivered rectangular impulses of 1 5 msec duration at twice diastolic threshold through an isolation unit Right ventricular pacing was similarly per formed using the lowest milliamperage which achieved reliable ventricular capture Refractory period studies were performed using the atrial extrastimulus method during which the cardiac cycle is scanned by introducing APD s at progres sively shorter coupling intervals until atrial refractoriness is reached

Electrocardiogram (ECG) Leads 1, 2 3, and/or V_1 high right atrial coronary sinus His bundle electrograms and time lines at 10 and 100 msec were displayed on a multichannel oscilloscopic recorder and relayed by a matching amplifier to a tape recorder Filter frequency settings between 40 and 500 Hz were used for intracardiac electro

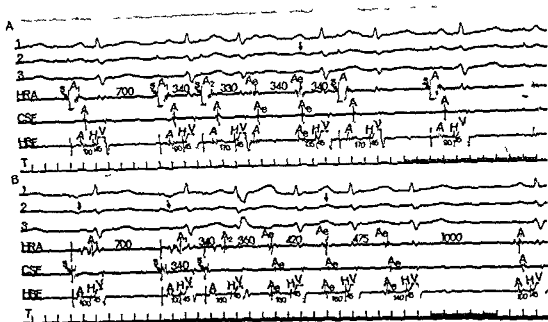


Fig 3 Sinus node re entry initiated by an APD from the high right atrium (*panel A*) and coronary sinus (*panel B*) Panel A the HRA was paced at a cycle length of 700 msec and A was introduced into the HRA 340 msec after the eighth paced beat Sinus node re entry resulted and was terminated by resumption of atrial pacing Panel B pacing the coronary sinus at the same CL and introducing A at the same coupling interval into the coronary sinus result in sinus node re entry The arrows in Lead 2 show the inverted P waves during CS pacing becoming upright during SNR Note also that during CS pacing the atrial electrogram in the CS precedes that in the HRA whereas during sinus node re-entry the normal high low sequence is present



Fig 4 Sinus node re entrant tachycardia resulting from continuous rapid atrial pacing at a CL of 460 msec The third atrial beat Ae occurs 90 msec prior to the stimuli is artifact (S) which is ineffective An accelerated atrial rhythm with normal activation and upright P waves results

tained phenomenon lasting several minute The cycle length of the tachycardias ranged from 320 msec to 625 msec In four patients 1 1 A V conduction was seen during the tachycardia while in the remaining two patients both 1 1 and A V nodal Wenckebach conduction were seen (Fig 6)

In all patients termination of the tachycardias occurred spontaneously In the two patients with sustained tachycardias termination was also accomplished by carotid sinus pressure Valsalva s maneuver properly timed single APD s and/or atrial overdrive pacing

One patient (MH) demonstrated both an SNR as well as a typical A V nodal re entrant tachycardia as illustrated in Fig 7 Note the low to high atrial activation sequence and inverted P waves in Lead II during the A V nodal re entrant tachycardia (panel *A*) and the high to low atrial activation sequence and upright P waves in Lead II during the sinus node re entry (panel *B*)

Discussion

Re entry within the region of the sinus node is a possible mechanism to account for the tachycardias observed in this study These tachycardias may be initiated when the requisite conditions for re entry (i e unidirectional block delayed con

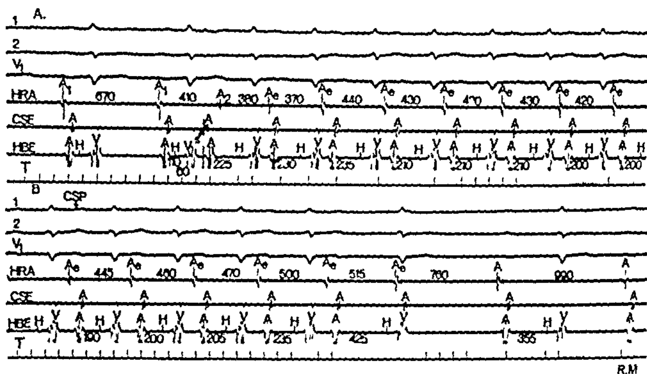


Fig 2 Termination of SNR tachycardia with carotid sinus pressure *Panel A* a premature impulse introduced in the coronary sinus during sinus rhythm arrives at the high right atrium at an A_1A_2 coupling interval of 410 msec A tachycardia consistent with sinus node re entry as previously described ensues and is sustained for several minutes (not shown) *Panel B* (noncontinuous with panel A) Carotid sinus pressure (CSP) is applied at the arrow and results in slowing of the tachycardia rate markedly prolonged A H intervals and eventual termination of the tachycardia Increased vagal tone persists after the tachycardia terminates as evidenced by slowed sinus rate and prolonged A H intervals CSF coronary sinus electrogram

tion sequence normal atrial activation, the atrial activity recorded in the high right atrial electro gram precedes the atrial activity recorded in the His bundle electrogram (low right atrial activity) Low to high activation sequence low right atrial activity precedes high right atrial activity

Unless otherwise stated all intervals were measured on the high right atrial electrogram

Results

Single atrial echo beats and sustained tachy cardias consistent with sinus node re entry were produced by closely coupled APD s (coupling in tervals 245 to 460 msec) introduced either into the high right atrium (HRA) (six out of six patients) or the coronary sinus (CS) (four out of four patients) at sinus rhythm or during basic paced atrial drive The A_1A_2 coupling intervals from the CS and HRA which produced sinus node re entry (echo zones) are given for each patient in Table II

Fig 1 illustrates a tachycardia initiated by a single atrial premature depolarization (A) intro duced at a coupling interval of 330 msec after a series of sinus beats The tachycardia is charac terized by an atrial cycle length of < 600 msec , a high to low sequence of atrial activation, and P waves similar to those of sinus origin Sponta neous termination of the tachycardia is followed by a long pause (1,140 msec) after which sinus rhythm resumes

Fig 2 shows the initiation of a SNR tachy cardia by a single APD introduced into the coronary sinus during sinus rhythm (panel *A*) and its termination by carotid sinus massage (panel *B*) Note the atrial activation sequence of the tachycardia is similar to normal sinus beats and clearly different from the APD (A_2)

In Fig 3, SNR tachycardias initiated by single properly timed premature atrial depolarizations introduced into the HRA during right atrial pac ing (panel *A*) and into the coronary sinus during coronary sinus pacing (panel *B*) are depicted

Sinus node re entrant tachycardias were also initiated by continuous atrial pacing in four patients (CL 350 470) and by continuous retro grade atrial capture from ventricular pacing in one patient (CL 300) Fig 4 demonstrates a tachycardia initiated by atrial pacing and Fig 5 demonstrates one initiated by ventricular pacing A high to low atrial activation sequence is seen in both tachycardias

The maximum duration of each patient s tachycardia ranged from seven beats to a sus

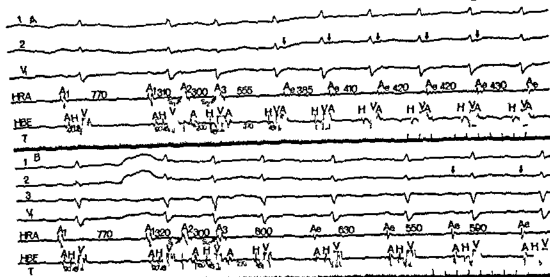


Fig 7 Induction of an A V nodal re-entrant tachycardia (*panel A*) and a sinus node re-entry tachycardia (*panel B*) in the same patient *Panel A* two premature stimuli S S at 310 and 300 msec respectively result in an A H of 370 msec after S sufficient delay to result in A V nodal re-entry Note the inverted P waves (arrows Lead 2) and the low high atrial activation sequence *Panel B* S S at 320 and 300 msec respectively results in an A H of only 270 msec after S insufficient delay in this patient for A V nodal re entry However a tachycardia with a high to low atrial activation sequence and upright P waves resulted The tachycardia lasted for 21 beats and terminated spontaneously The average cycle length of 625 msec was considerably shorter than the patient s sinus rate The 800 msec. interval between A and Ae is discussed in the text

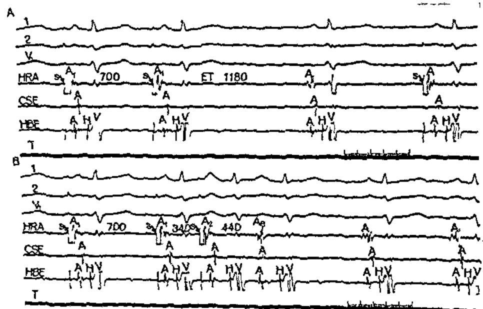


Fig 8 Differentiation of sinus node re-entry from sinus node escape beats after paced atrial cycles *Panel A* Atrial pacing at an A A cycle length of 700 msec is discontinued after eight consecutive paced beats without the introduction of an atrial premature beat The sinus escape time (ET) is 1 180 msec *Panel B* at the same paced atrial cycle length a premature beat (A) is introduced 340 msec after the eighth paced beat and is followed by an atrial beat (Ae) which is consistent with sinus node re-entry The A Ae interval of 780 msec is considerably shorter than the sinus node escape time thus eliminating the expected sinus escape beat as the mechanism for Ae

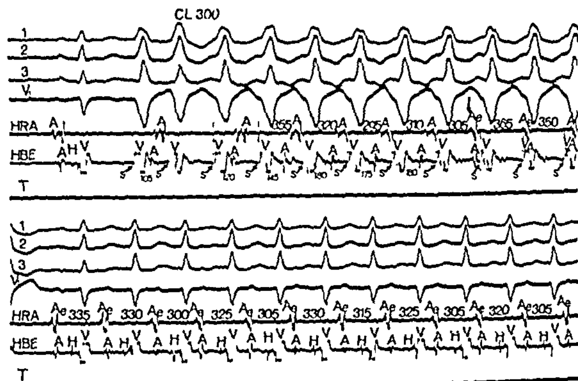


Fig 5 Panels *A* and *B* are continuous Rapid ventricular pacing results in retrograde atrial activation via retrograde A V nodal Wenckebach cycles Antegrade atrial activation consistent with sinus node re-entry begins at the arrow A sustained tachycardia follows which is better appreciated after the stimulus is discontinued (*panel B*)

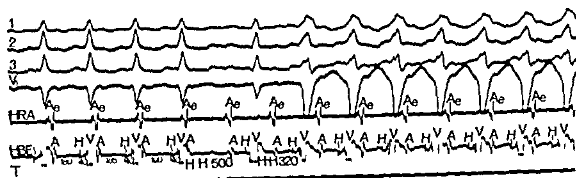


Fig 6 A V nodal Wenckebach type of conduction occurring during a sinus re-entrant tachycardia Following block of the fourth P wave in the A V node the R R interval increases The H H interval measures 500 msec which shortens to 320 msec following resumption of A V conduction The acute change in H H cycle length results in aberrant conduction of a left bundle branch block (LBBB) type

duction, and recovery of excitability) are present in the region of the sinus node A premature impulse may arrive at the region of the sinus node during its relative refractory period be blocked along one front enter at another site conduct slowly through relatively refractory tissue, and finally exit to re excite the atrium [5] Alternately a premature impulse, without entering the sinus node per se might encounter conduction delay within a perinodal zone having a longer refractory period than adjacent atrial tissue,[11] and then result in reciprocation between the atrial myocardium and the perinodal zone However the long pause following termination of the tachycardia seen in our cases suggests that the sinus node was depolarized during these tachycardias Similarly a properly timed premature atrial impulse may leave the perinodal zone relatively refractory to a subsequent sinus node impulse generated either on time or earlier than expected due to an electrotonic influence of the premature impulse on the sinus pacemaker [14, 15] In either case the sinus node impulse could result in a delayed atrial depolarization due to conduction delay in the

as seen during stimulation within the atrial vulnerable period can be excluded since stimuli delivered to different sites (HRA or CS in Fig 3 ventricle or atrium in Fig 5) resulted in similar appearing tachycardias Also the absence of prolonged intra atrial conduction (e g CS to HRA) argues against a local phenomenon as the mechanism for tachycardias in these patients Shift and acceleration of the pacemaker within the sinus node perhaps due to stretch from radial deformation of the node after an early APD are alternative mechanisms which cannot be excluded Acceleration and pacemaker shift within the sinus node of the isolated right atrium of the rabbit were attributed to the electrotonic effects of the APD by Bonke and co workers[14 15] However the brief periods of sinus acceleration i e only one sinus cycle reported by these authors could not account for the long periods of sinus acceleration and the abrupt termination of the tachycardias in the patients we studied

An alternative mechanism which may be considered is one that involves specialized internodal tracts within the atrium Such specialized tracts have been demonstrated anatomically[2] and some investigators have shown increased conduction velocity along certain anatomic landmarks *within the atrium*[3] In our cases, since the premature beats which initiate the tachycardias fall within the relative refractory period of the A V node they may re enter from the A V node and travel retrogradely to the sinus node via one of the internodal tracts without exciting the atrium Subsequent activation of the atrium would then occur in an antegrade direction representing an unusual form of A V nodal re entry rather than sinus node re entry However as concluded by Spach and co workers there is no electrophysiologic evidence at present (except perhaps when potassium levels are abnormally high) to conclude that these specialized pathways are insulated electrically from the surrounding tissues with the ability to conduct impulses to the exclusion of atrial muscle We therefore think that sinus node re entry represents a more attractive hypothesis for the tachycardias observed

Sinus node re entry and A V nodal re entry have common characteristics in that both may be initiated and terminated by premature stimuli, both may be initiated by rapid pacing and both may terminate by maneuvers which increase vagal tone The distinction between these two types of tachycardia may be made on the basis of (1) the sequence of atrial activation from the high to low right atrium in sinus node re entry and the reverse during A V nodal re entry and (2) upright P wave morphology in Leads 2 3 and aV_F during sinus node re-entry tachycardia with inversion in these leads during A V nodal re entrant tachycardia In both forms of tachycardia the initiating premature atrial beat occurs during the relative refractory period of the A V node resulting in a prolonged A H interval Initiation of an A V nodal re entrant tachycardia is dependent upon the attainment of a critical delay in A V nodal conduction while in sinus node re entry it is not Experimentally it has been demonstrated that the more important determinant of sinus node re entry is the arrival time of the APD in the sinus node region and the A H prolongation is merely a result of the prematurity of A[6] Furthermore sinus node re entry can result when an APD occurs during the effective refractory period of the A V node whereas A V nodal re entry is extremely uncommon under these same circumstances[2]

While in general we believe that sinus node re entry in man may be demonstrated experimentally relatively often the spontaneous occurrence of a sinus node re entrant tachycardia appears to be *less frequent* In clinical tracings inability to *distinguish* P wave morphology i e upright or *inverted* may make the distinction between sinus node re entry and A V nodal re entry difficult Periodic A V block may allow P wave morphology to be observed but electrophysiologic studies with intracardiac recordings may be necessary to distinguish these two types of re entry

Summary

Sinus node re entry (SNR) usually appears as a *single* beat Tachycardias (SNRT) consistent with sustained SNR were seen in six patients and were initiated by premature stimulation of the high right atrium (six patients) and coronary sinus (four patients) and after continuous pacing from the high right atrium (four patients) or right ventricle (one patient) at rates of 130 to 200 per minute During SNRT (1) atrial beats exhibited a high to low atrial activation sequence (2) the P waves were similar in morphology to P waves during sinus rhythm and (3) re entry in the A V node or at the site of stimulation could be ex

perinodal zone and simultaneously reciprocate within the perinodal tissue producing a sinus node re entrant beat(s) The first atrial response of this tachycardia would represent a delayed sinus beat and the second atrial response would represent the first echo ' beat of the re entrant tachycardia (this mechanism could explain the long A_3A_e interval in Fig 7)

As demonstrated in this study, rapid continuous pacing either of the atrium or of the ventricle with retrograde atrial capture, may also result in sinus node re entry Wenckebach type of conduction may occur in the sinus node region under these conditions and the mechanism for sinus node re entry would be analogous to that for A V nodal re entry occurring during A V nodal Wenckebach cycles[18]

In light of the above postulates we may now examine the criteria by which ' early ' responses to APD s have been classified as sinus node re entry When premature atrial impulses are introduced at progressively shorter coupling intervals a variety of A A_3 return cycles results[17] Premature impulses introduced a long coupling intervals result in A_2A_3 intervals which are compensatory resulting from collision of the premature impulse with the emerging sinus impulse At shorter coupling intervals resetting of the sinus pacemaker occurs so that A_2A_3 intervals equal the sum of conduction time of A_2 into the sinus node a sinus cycle (A_1A_1) and conduction time out of the sinus node assuming that no depression of the sinus node occurred Further prematurity of A_2 may result in sudden shortening of the A_2A_3 interval so that A_1A_3 now approximates A_1A_1 When A_1A_3 equals A_1A_1 sinus node entrance block[1] could exist and, if there is only one postextrasystolic beat it is difficult to differentiate sinus node entrance block from a single sinus node echo beat fortuitously occurring 'on time Experimental models of sinus node re entry in which the re entrant beats were usually single have therefore required A_1A_3 intervals clearly shorter than A_1A_1 intervals as a criterion for sinus node re-entry On the other hand, when a tachycardia occurs A_1A_3 intervals may equal or exceed A_1A_1 intervals since the subsequent tachycardia indicates that a process other than (or in addition to) entrance block is occurring

Therefore we propose the following criteria for sinus node re entry

During sinus rhythm (1) Within a given range of A_1A_2 intervals, a premature atrial depolarization (A_2) results in a postextrasystolic return cycle (A_2A_3) which is unexpectedly short When the sum of the pre extrasystolic (A_1A_2) and the postextrasystolic (A_2A_3) intervals is less than the shortest sinus cycle length (A_1A_1), the A_3 response is best explained on the basis of re entry in the sinus node region If the sum of A_1A_2 and A_2A_3 is longer than the A_1A_1 the origin of A_3 will be less certain unless a tachycardia results even though a single A_3 response may still represent a sinus node echo

(2) The activation sequence of the atrial echo beat (A_3) is the same as for sinus beats i e from the high to low right atrium

(3) The P wave configuration of A_3 as recorded on the standard ECG leads is similar to that of sinus beats

(4) The above criteria apply irrespective of the atrial site at which A_2 is introduced (high right atrium, coronary sinus etc)

(5) The occurrence of three or more successive atrial echo beats $(A_3\ A_4\ A_5\ A_6$ etc) at cycle lengths of $\leq$ 600 msec constitutes a tachycardia Accelerated rhythms with a cycle length $>$ 600 msec may also be seen

(6) A tachycardia can be terminated by a properly timed APD

During paced atrial cycles During paced atrial drive rates all of the above criteria apply to the diagnosis of sinus node re entry However the sum of the pre and postextrasystolic intervals (A_1A_3) can be greater than the A_1A_1 interval but must be significantly less than the sinus node escape time (see Fig 8)

As in all previous in vivo studies of sinus node re entry, the exact site of re entry whether in the sinus node per se, in the perinodal zone or in the adjacent atrial tissue cannot be stated for certain In addition atrial electrical events may fail to reflect sinus nodal events[19] What may be inferred however is that the general region of re entry seems to be high in the right atrium in or about the sinus node since the atrial activation sequence occurs in a normal high to low fashion Slight differences in morphology of the P waves during re entry may be due to different exit sites from the sinus node and/or rate dependent atrial aberration[6]

Alternative mechanisms for accelerated sinus beats have been reviewed by Paulay Varghese and Damato[9] A purely local phenomenon, such

Sinus node re entry and sinus node tachycardia

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The occurrence of echo beats in human hearts is a well recognized phenomenon and has been demonstrated to be one of the mechanisms for supraventricular tachycardia Bundle of His recordings in human hearts have clearly demonstrated that the site of re entry can be within the A V node or in the His Purkinje system (HPS)[1] Animal experiments have indicated that the re entry can also occur in the sinus node (SN) and can possibly be a mechanism for reciprocating tachycardia[3,5] Recently Paulay Varghese and Damato reported their observations on the effect of early atrial depolarization in man and found SN re entry in some of their cases Our present report deals with five cases in whom SN echoes could be demonstrated with the extrastimulus technique In one of them such echoes were responsible for initiating reciprocating tachycardia Such attacks were also noted to occur spontaneously in the laboratory

Materials and methods

Four patients were subjected to cardiac catheterization primarily for hemodynamic studies His bundle electrograms (HBE) were obtained after completing these studies The fifth patient was catheterized primarily for conduction studies as he had bifascicular block following repair of a ventricular septal defect The clinical and electrocardiogram findings are listed in Table I

Technique The recordings were performed in the postabsorptive state under demerol phenergan and sparine sedation Informed consent was obtained from the parents None of these patients were on cardioactive drugs at the time of study The recordings were made on photographic paper using Electronics for Medicine multichannel recorder HBE were obtained via a tripolar catheter placed near the tricuspid valve[7] A quadripolar catheter was positioned against the lateral wall of the right atrium (RA) The two distal poles were used to record high right atrial electrograms (RAE) and the two proximal poles to deliver stimuli to the RA Leads I II and III were recorded simultaneously All stimuli were delivered to the RA through a Grass Stimulator Model DS88 The RA was paced by a basic pacing stimulus (S_1) at the slowest possible rate producing stable capture without sinus escape beats Extrastimulus (S_2) technique was used to study SN function[8] The S_2 was delivered in late diastole and moved progressively earlier in 10 to 20 msec decrements until the effective refractory period of the atrium was reached In each test cycle the basic stimulus (S_1) following the S_2 was omitted to recognize the occurrence of A V junctional or SN echoes prior to sinus escapes A H and V following S will be referred to as A H and V respectively and the A H and V following S_2 will be referred to as A_2, H and V_2 respectively The return cycle or sinus escape interval (SEI) is the time between A_2 and the following sinus A wave The A H and V of the return cycle will be designated as A_3 H_3 and V_3 respectively To evaluate the expected time of the appearance of A_3 sinus node recovery time or SEI at the basic pacing rate was measured at least three times in each patient In none of the patients was the SEI shorter than the basic S_1S_1 interval The following terms have been used in the text[8] (1) reset Resetting of SN is said to occur when the

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cluded The cycle length of SNRT ranged from 625 to 320 msec and SNRT either terminated spontaneously (six patients) or after premature atrial capture and/or vagal maneuvers (two patients) The electrophysiologic characteristics of SNRT and differentiation of SNRT from A V nodal re entry are discussed

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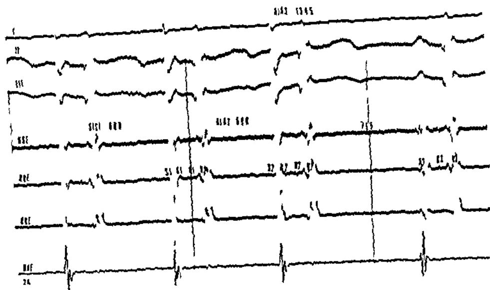


Fig 2 A Patient No 2 Panel A shows resetting of SN

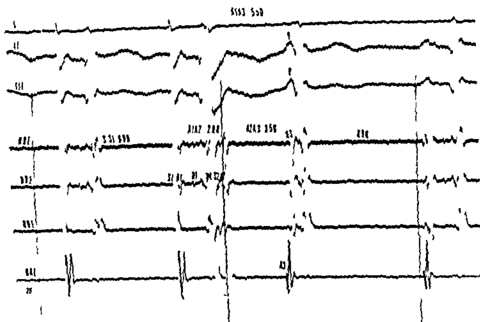


Fig 2 B Patient No 2. Panel B shows SN echoes which are blocked proximal to HB

for a reciprocating tachycardia Basic atrial pacing was performed at 600 msec cycle length The SEI ranged from 655 to 900 msec At A_1A_2 interval of 590 msec the SN is reset (Fig 2 *A*) Reset occurred up to 290 msec delay At 270 msec delay the A A_2 interval suddenly shortened to 200 msec with an A A interval of 560 msec This interval is shorter than the basic pacing interval and the SEI The P waves were not clearly seen at this coupling interval However they are unquestionably upright in Leads II and III at subsequent test cycles (Figs 2 *B* and *C*) The high RA is activated earlier than the low RA There was a definite echo zone from 270 to 200 msec At 250 msec delay the SN echo produced a presumably reciprocating tachycardia There are three SN echoes seen in Fig 2 C The P wave in A_4 appears to be biphasic and one can argue that

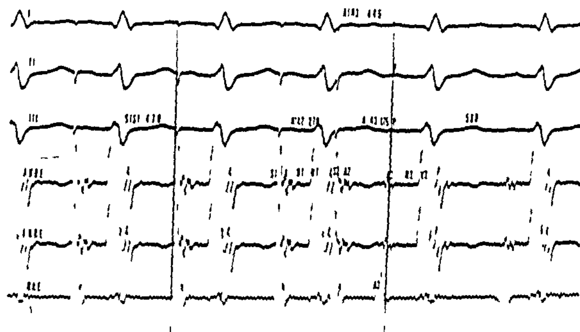


Fig 1 Patient No 1 Leads I II and III are simultaneously recorded with two HBF and RAE The A waves in HBF represent activation of low RA S_1S interval represents the basic pacing rate The numbers in Lead III represent the cycle length of the basic pacing rate the coupling interval and the return cycle The number above Lead I represents the sum of the test cycle (A A_1) and the return cycle (A_1) is an SN echo Note the upright P waves in Leads II and III and the earlier appearance of the A wave in RAE than in HBE

Table 1 Summary of clinical and electrophysiologic data

No	Patient	Age and Sex		Diagnosis	ECG	Basic drive (S S/min)	SEI range (msec)	Echo zone (msec)
1	JT	11 yrs	M	PORBB+ LAD	RBBB + LAD	125	515 960	2[illegible]0-[illegible]90
2	GN	10 yrs	M	Normal heart	Normal	100	655 900	270 200
3	MC	2 yrs	F	ASD + PDA	IRBBB	115	555 705	240-210
4	AK	14 yrs	M	AI	LVH	95	750 850	2[illegible]0-2[illegible]0
5	BD	11 yrs	M	AI	LVH	110	600 720	260-230

M male F female PORBB + LAD postoperative right bundle branch block with left axis deviation AI aortic insufficiency ASD atrial-septal defect PDA patent ductus arterio us

postectopic pause or return cycle (A_2 A_3) equals or exceeds SEI (2) complete interpolation The sinus escape beat or A_3 appears as it would have in the absence of S_2 (3) incomplete interpolation appearance of A_3 is delayed but the return cycle (A -A_1) is still shorter than the SEI and (4) SN echoes A_3 appears earlier than it would have in the absence of S

Results

All five patients demonstrated SN echoes following extrastimulation of RA All had a definite echo zone (Table I)

Fig 1 is a representative tracing from patient No 1 He was paced at 470 msec cycle length and his SEI ranged from 550 to 705 msec Resetting of SN occurred up to a coupling interval of 290 msec At the coupling interval of 270 msec the effective refractory period of the A V node is reached as A_2 is not conducted to HB A_2 is followed by a beat which is an SN echo because (1) The A A_3 interval is only 175 msec and A_1A_3 only 445 msec which is shorter than the basic pacing cycle length S_1S_1 (470 msec) and also shorter than SEI (550 to 705 msec) (2) P waves are upright in Leads II and III (3) The sequence of atrial activation is from high RA to low RA (4) There is a definite echo zone ranging from 270 to 220 msec The prolonged A_1H_1 is due to antegrade concealed conduction of A_2 The effective refractory period of atrium was reached at 200 msec

In Case No 2 the SN echoes were responsible

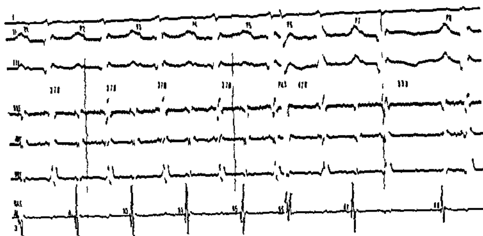


Fig 3 It is a tracing from patient No 9 during a spontaneous attack on SN tachycardia (rate of 160 per minute) The P waves are upright in Leads II and III and A waves appear earlier in RAE than in HBE The numbers between Lead III and HBE represent the cycle length between the subsequent A waves A properly timed APD captures the atrium (A_s) and terminates the tachycardia

to pace the heart to insure a constant basic cycle length which otherwise may be variable due to sinus arrhythmia in children A short return cycle may be caused by incomplete or complete inter polation[9] or by an SN echo[4] Incomplete interpo lation occurs when the APD only partially enters the SN and fails to reset it The next sinus *impulse (A_3) is* generated at the expected time but progresses slowly and though the return cycle is short the A A_3 interval is longer than the SEI

In complete interpolation an APD does not gain access to SN which is *not reset*[3, 1, 12] Strauss and Bigger[3] have assumed a zone of perinodal fibers which could possibly serve as a site of block of such early APD s The next ensuing sinus impulse occurs as if S_2 *were absent* Thus interpolation results in a short return cycle and the A_1A interval equals the SEI

With echoes the return cycle is very short and the A A interval is shorter than SEI The site of re entry could be through the A V node HPS or SN The most important clues as to the site of re entry are (1) the sequence of atrial activation in RAE and HBE (2) configuration of P waves in Leads II III and aV_F (3) relation of echoes to critical delay in the A V node or in the HPS

When re-entry occurs through the A V node or HPS the low RA is activated earlier than the high RA due to retrograde activation As a result the P waves in Leads II III and aV_F are inverted Moreover, re entry through the A V node or the HPS is related to the critical delay in these structures[2, 1] In all our cases the sequence of atrial activation is from high to low RA P waves could be clearly seen in two cases and were upright in Leads II and III in both In the remaining three cases the P waves were sub merged in QRS complexes In none of these cases however was the re entry related to a specific delay in the A V node or HPS

In case No 2 attacks of reciprocating tachy cardia through the SN could be experimentally induced and also occurred spontaneously in the laboratory The diagnosis of SN reciprocating tachycardia is confirmed by the following evidence (1) it was initiated by an SN echo (2) there was a definite echo zone and APD s occur ring in this zone produced either SN echoes or reciprocating tachycardia (3) an appropriately timed APD terminated the attack

Han Malozzi and Moe[3] demonstrated SN reciprocation in the rabbit heart and concluded that an APD may fail to engage one margin of the SN enter another site and travel through the SN so slowly that the atrium has recovered in time to respond again to the emerging stimulus For re entry to occur the premature stimulus must find part of the tissue refractory and part excitable The conduction must be slow enough to allow the tissue that is to be re excited to recover from its refractoriness Evidence of dissociation in

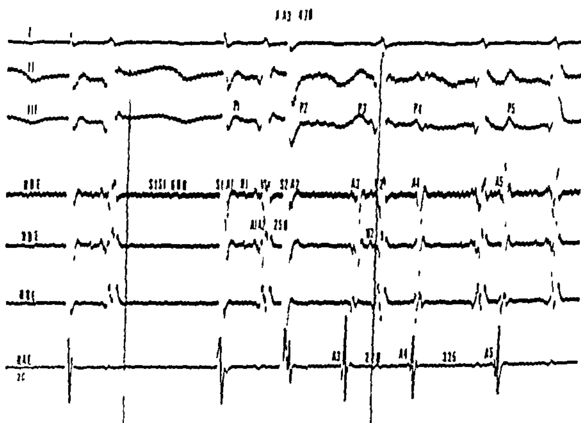


Fig 2 C Patient No 2 Panel C shows a series of three SN echoes (A ,A ,A) The numbers in the lowest tracing represent the cycle length between these echoes See text for details

it is an A V junctional echo However, the pattern of atrial activation is from high to low RA and, therefore it is more likely to be an SN echo In the laboratory this patient had several spontaneous attacks of presumably reciprocating tachycardia (rate of 160 per minute) The P waves were upright in Leads II and III with high RA activated earlier than low RA which is highly suggestive of re entry through SN They could be easily terminated by a single atrial premature depolarization (Fig 3) or with multiple premature stimuli delivered at slower rate than the tachycardia

To demonstrate that the echoes were not related to the delay in A V node the AH intervals at fixed atrial pacing producing Wenckebach block were compared with the A H_2 intervals following S_2, which produced the SN echoes Fig 4 is from patient No 3 SN echoes were observed at coupling intervals of 240 230, 220 and 210 msec (panel A) The A H_2 intervals at these coupling intervals were 225 230 240 and 260 msec Atrial pacing at 180 per minute produced 9 8 Wenckebach block (panel B) Though the AH lengthened from 105 to 270 msec no echoes are observed This confirms that the echoes in panel A are not A V junctional echoes None of the echoes were related to the specific delay in HPS as the H_2V_2 interval remained constant in all cases

Discussion

The rarity of demonstrating SN echoes may be due to difficulties in studying sinus node function in the human heart In 1962 Langendorf and co workers[9] presented a case with atrial parasystole in which they ascribed shortening of the return cycle to interpolation and postextrasystolic sino atrial conduction delay Recently the technique of extrastimulation of the atrium has been utilized to study the SN function in the human heart[6,8,10] Such work has enabled us to understand the mechanism of short and long returning cycles

When an atrial premature depolarization (APD) falls in atrial diastole it usually penetrates discharges and resets the SN In this situation, the return cycle equals or exceeds the SEI Other factors which may influence the duration of the return cycle are postectopic depression of automaticity, sinoatrial conduction delay or block or both[4,10,11] In our studies the SEI was measured repeatedly in each case, since it varied from time to time However at no time was it shorter than the basic driving rate We preferred

shorter than the SEI (2) upright P waves in Leads II and III (3) activation of high RA preceding the activation of low RA (4) lack of relation to critical delay in the A V node or HPS (5) definite echo zone In one of the cases attacks of reciprocating tachycardia through the SN occurred spontaneously and also could be initiated by an SN echo These were terminated by a single APD or by atrial pacing

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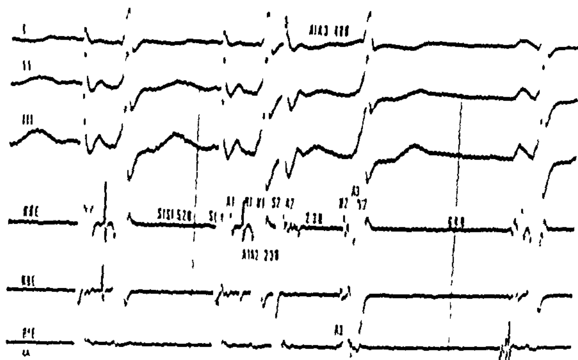


Fig 4 A Patient No 3 SN echoes are seen in panel A (A_1) Numbers between A_1 and H_1 represent the A H interval



Fig 4 B Patient No 3 Panel B shows pacing at fixed rate of 180 per minute which produces 9 8 Wenckebach cycles The numbers in the lower HBE represent the AH interval which has progressively prolonged from 105 to 270 msec S_9 is blocked proximal to HB See text for details

A V node has been demonstrated in the rabbit heart by Han Malozzi and Moe [3] In a recent review of atrial tachyarrhythmias by Wellens [15] there was no case where SN re entry could be a mechanism for atrial tachycardia However, it would appear that at least some of the atrial tachycardias use the SN as a path for re entry If an impulse can re enter the atrium through the SN once there is no question that this re-entry can be self sustaining This has been clearly shown in one of our cases However the incidence of such an arrhythmia in clinical practice is yet to be determined

Summary

Five patients are reported with SN echoes which could be produced by the technique of APD The RA was paced at the basic rate and the SEI was measured repeatedly SN echoes were diagnosed on the basis of (1) A_1A_3 interval

Table I Summary of data

	Day 1		Day 2		Day 7		
	Mean	*S D*	*Mean*	*S D*	*Mean*	*S D*	
A/E (15%)	17.2	8 42	1o 7	9 37	18 1	9 53	A.C I
	19 2	10 93	21 1	12 63	20 3	11.35	A M I
PEP corrected (0 08 to 0 11 sec)	*137.8*	*17 16*	*136 9*	*16 69*	138 6	16 70	A C I
	130 7	9 16	135 7	7.24	135 3	8 23	A.M I
LVET corrected (0.39o ± 0 013 M 0 415 ± 0 011 F sec)	394 6	30 71	*392 2*	*28 65	39? 0	2o 0	A C I
	399 6	25 50	386.3	23 19	402 1	20 02	A M I
PEP/LVET (0 346 ± 0 010)	41 2	10 01	41 1	8 83	41 8	*9 87*	A C I
	37 8	5 56	42 3	7 11	38 8	5.24	A M I

patient in the left lateral decubitus position during quiet normal respiration Values were obtained by averaging 20 consecutive cycles at 100 mm per second paper speed As further information became available over the next few days the patients were placed in either the acute coronary insufficiency or the acute myocardial infarction group on the basis of serial clinical ECG and serum enzyme studies

From the resulting records the pre ejection period (PEP) the corrected left ventricular ejection time (LVET) and total electromechanical systole (QS_2) were measured and/or derived The PEP/LVET ratio was calculated in the usual manner from the above values Recently this ratio has been shown to constitute a useful index of left ventricular performance encompassing the two major subintervals of total electromechanical systole and not requiring correction for rate The actual values of the measured time intervals were corrected for rate using previously derived regression equations of Weissler In the apexcardiograms the a/E ratios were calculated as suggested by Benchimol and Diamond [7]

Results

1 Abnormal a/E ratios were noted in all patients with acute myocardial infarction AMI and acute coronary insufficiency (ACI) but on none of the three days of the study were there any statistically significant differences between the two groups (Table I)

2 The pre-ejection period (PEP) (Fig 1) was found to be prolonged in patients with either AMI or ACI with the use of Weissler's[1] normal figures (0 07 to 0 12 sec) However although all

Table II LVET

	Weissler	Day 1	Day 2	Day 7
Mean	413 0	394 5	390 3	396 2
S D	10	27 36	27 01	24 03
No of patients	1?1	28	27	20

values in our patients were consistently abnormal, they showed a great deal of overlap and could not be used in individual patients in the differentiation between ACI and AMI on any one of the three days of the study

3 The corrected left ventricular ejection time ($LVET_c$) (Fig 2 and Table II) showed statistically significant differences in mean values ($p < 0 01$) between the patients with ACI and those with AMI the differences being most striking on day 2 of the study However the degree of overlap between the values in individual patients was such as to preclude the use of this parameter in a discriminative or predictive capacity It would appear therefore that it is impossible to distinguish patients with ACI from those with AMI by means of the LVET

4 There was no significant difference in the PEP/LVET ratio in the two groups of patients on any of the three days of the study (Fig 3) however both groups of patients showed a significant increase in this ratio in comparison with Weissler s normals In other words the ratio of PEP/LVET was increased in both ACI and AMI but allowed for no discrimination between these two conditions

Careful follow up of the two groups of patients in this study has yielded no useful information

Left ventricular function in ischemic heart disease
Assessment by noninvasive techniques

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The systolic time intervals, as determined by simultaneous phonocardiography, electrocardiography and carotid pulse recordings have been extensively employed during the past few years in the noninvasive evaluation of left ventricular function This also applies to the procedure of apexcardiography

Characteristic changes in the systolic time intervals have been described in patients with congestive heart failure,[1] acute myocardial infarction,[2] angina pectoris,[3] and aortic valve disease [4] It has been demonstrated that the systolic time intervals constitute a valid index of myocardial contractility that they are of assistance in following patients with disease confined to the left ventricular myocardium, and that they aid in the assessment and follow up of patients with extramyocardial hemodynamic lesions of constant severity [5] This being the case we felt that it might be useful to determine whether or not the systolic time intervals or the apexcardiogram or both, can be of value in the early differential diagnosis of acute coronary insufficiency* from acute myocardial infarction in a series of patients admitted to a coronary care unit Our interest was further stimulated by the previous demonstration[3] that a direct relationship exists between the "a wave amplitude in the apexcardiogram and the left ventricular end-diastolic pressure For this reason, we also recorded the a/E ratios in the apexcardiograms of this same group of patients

Thirty two patients, ranging in age from 40 to 86 years (mean, 63 years) were studied within 24 hours of the onset of acute symptoms There were 29 men and 3 women in the group Fourteen patients were restudied within 48 hours and 16 of the original group were restudied on the seventh day after the onset of symptoms The criteria for inclusion in the study were (1) a history of retrosternal chest pain suggestive or characteristic of myocardial ischemic pain and (2) electrocardiographic (ECG) changes suggestive of acute myocardial infarction or subendocardial ischemia Patients with intraventricular conduction defects, atrioventricular block diastolic hypertension, or clinical evidence of aortic valvular dysfunction were excluded Also omitted were patients who had recently received digitalis, diuretics, propranolol atropine or vasopressors An Elema Schonander piezo microphone (EMT 258) with a low frequency (20 to 30 Hz) band pass filter (EMT 28) were used to record the heart sounds An Elema Schonander pick up (EMT (510C) fitted under a Marey capsule was used to detect the apex pulse and the carotid pulse was recorded with a Siemens Infraton' pulse pick up These and the ECG tracing were recorded on an Elema Schonander Mingograf recorder This instrumentation has a time constant of 2 0 sec for the apexcardiogram and 1 0 sec for the carotid pulse tracing with a flat output response between 1 and 60 Hz

All recordings were made at 11 A M with the

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*The designation "acute coronary insufficiency as used in this report follows the terminology of Paul Wood and is described as prolonged ischemic cardiac pain without electrocardiographic or biochemical evidence of acute myocardial infarction

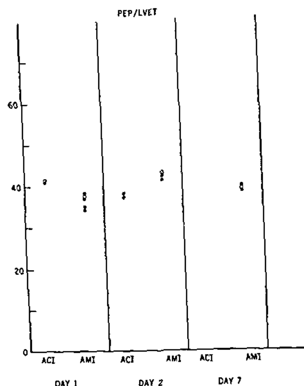


Fig 3 PEP/LVET ratio Open circles represent the mean values.

and in parallel with the findings at cardiac catheterization we had hoped to be able to differentiate acute myocardial infarction from acute coronary insufficiency by such techniques However as indicated above we found the corrected PEP to show a considerable overlap between the two groups with the mean values showing no statistically significant differences (Fig 1) We were also unable to demonstrate any statistically significant differentiation between our values and Weissler s normal values for PEP_c. This is in keeping with the data reported by Boughner[8] Heikkila[9] and Hodges and their co-workers

The LVET although showing the above described overlap was still helpful in making the distinction between the two groups if mean values only were considered In addition when compared with Weissler s normals there was a significant shortening of LVET on all three days of the study (Table II) This is in agreement with the results reported by Diamond[2] Heikkila[10] Hodges[1] Schoenfield[12] and Wayne[3] and their colleagues The ratio of PEP/LVET as indicated above was of no assistance in separating those patients with acute coronary insufficiency from

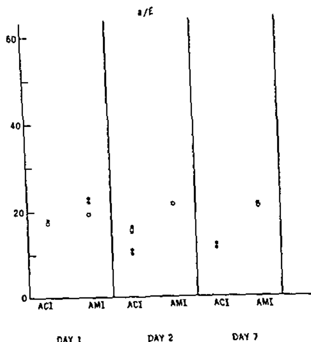


Fig 4 Apexcardiogram a/E ratio Open circles represent the mean values.

those with acute myocardial infarction In both groups the ratio PEP/LVET was increased but without statistically significant difference be tween the two groups

The results of the apexcardiography study (Fig 4) may be summarized by the statement that the a/E ratios were not of assistance in the early differentiation between acute coronary insufficiency and acute myocardial infarction

Summary

1 Thirty two patients (29 men and 3 women) admitted to a coronary care unit with either acute coronary insufficiency or acute myocardial infarction had their systolic time intervals and the a/E ratio of the apexcardiogram studied on days 1 2 and 7 of their hospital stay

2 Only the LVET and PEP/LVET were found to undergo any statistically significant change Although all figures were in the abnormal range they had no discriminative value in individuals None of the other commonly accepted noninva sive indices of left ventricular function including the a/E ratio of the apexcardiogram were found to be of assistance in the early distinction between acute coronary insufficiency and acute myocardial infarction

We gratefully acknowledge the assistance of Mr David Leung Senior Technologist and of the Department of Epidemiology and Biostatistics of the University of Toronto

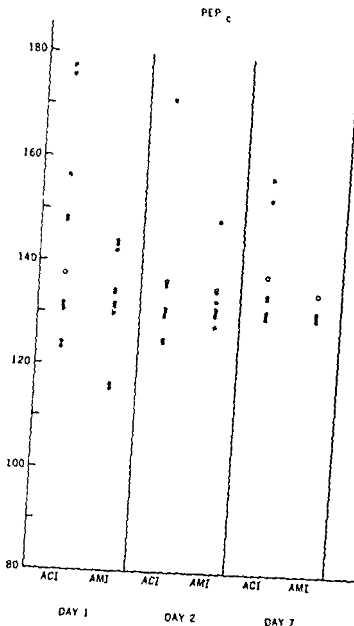


Fig 1 The pre ejection period *PEP*, corrected PEP *ACI* acute coronary insufficiency *AMI* acute myocardial infarction Open circles represent the mean values

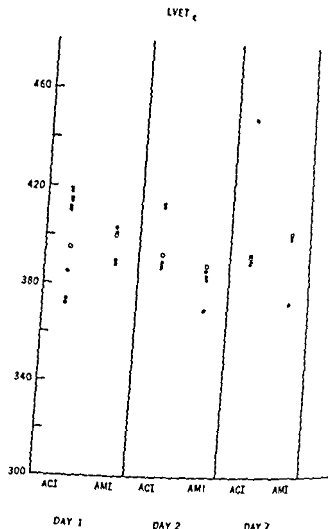


Fig 2 Left ventricular ejection time *LVETc* corrected LVET Open circles represent the mean values

In the ACI group (14 patients) one patient died suddenly at home from an acute myocardial infarction while awaiting his turn for aortocoronary bypass surgery and permission for necropsy was not obtained In the AMI group (18 patients) there have as yet been no deaths although one patient had a nonfatal cerebrovascular accident

Discussion

Benchimol and Diamond[7] reported a significant increase in the a/E ratios in coronary artery disease and showed a direct correlation between the LVEDP and this ratio We were therefore able to corroborate their findings but, as indicated above we were unable to show any discriminative characteristics in this ratio between patients with acute coronary insufficiency and those with acute myocardial infarction The systolic time intervals (PEP LVET and PEP/LVET) had previously been shown to be significantly related to the ejection fraction (EF) and the end diastolic volume (EDV) the closest correlation having been shown between the PEP/LVET and the EF by Garrard Weissler and Dodge[6] Leonard and associates[8] further showed this to be true for steady state conditions and during acute interventions

It was suggested by Weissler and associates[9] that the systolic time intervals could be used as a valid index of myocardial contractility, which should prove useful in comparing patients with different forms of left ventricular dysfunction Since our noninvasive measurements had deviated from Weisslers values,* simultaneously

* There is much controversy regarding true normal values for STI[16] However we had previously investigated 20 normal individuals, and our values had deviated only slightly from Weissler s published figures. We therefore elected to use the latter as our standard

The natural history of uncomplicated valvular pulmonic stenosis

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Materials

Sixty eight patients with a diagnosis of uncomplicated valvular pulmonic stenosis established by cardiac catheterization were studied Patients with additional cardiac defects were excluded from this study All 68 patients had initial and repeat cardiac catheterization The pulmonary artery was entered in all 68 patients A pressure gradient of at least 20 mm Hg across the pulmonary valve was considered essential to include these patients in the study Absence of significant changes in oxygen saturation supported by appropriate angiography excluded shunts of any kind Angiographic visualization of the pulmonary valve was performed in all cases

None of the 68 patients had cyanosis congestive heart failure or any other cardiorespiratory problems Clinically they presented with typical physical signs of isolated pulmonic stenosis with varying degrees of right ventricular hypertrophy on the electrocardiogram Cardiac catheterizations were performed in all these cases mainly to establish the severity of the stenosis

These 68 patients were classified into two groups Group I comprised 37 patients who were less than one year of age at the time of first catheterization Their ages ranged from 11 days to one year with an average of six months (Table I) Group II comprised 31 patients who were more than one year of age on the initial study Their ages ranged from 1 5 years to 11 years with an average of five years (Table II) At the time of repeat cardiac catheterization studies the minimal range in Group I was 1 5 years with the maximal age being 12 years and the average five years In Group II the minimal age was 3 5 years maximal age 20 years and average age 10 years None of the 68 patients underwent surgery between the two cardiac catheterizations

Results

Right ventricular pressure Table I shows the right ventricular pressures in millimeters of Hg in Group I and Table II shows the same in Group II at both initial and repeat cardiac catheterizations These patients for simplification were divided into mild moderate or severe stenosis (Table III) Patients who had a right ventricular pressure of 60 mm Hg or less were considered mild Those with a right ventricular pressure between 60 to 100 mm Hg were considered moderate and the remaining patients who had a right ventricular pressure of over 100 mm Hg were considered severe In Group I at initial study there were 15 patients with a right ventricular pressure of under 60 mm Hg 17 who had right ventricular pressure between 60 and 100 mm Hg and five patients with a right ventricular pressure of more than 100 mm Hg (Table III) On repeat study only six of the 15 patients who were mild at initial cardiac catheterization had remained mild the remaining nine had increased in severity Of the 17 patients with moderate stenosis some had become severe and others had remained moderate in severity The number with moderate stenosis at repeat cardiac catheterization had remained the same namely 17 because some of the mild cases had become moderate and increased the number in this group The number of patients with severe stenosis had increased from five to 14 at repeat study

The following features are shown by the above findings Those patients with mild stenosis whom you would ordinarily not consider surgical candidates can increase in severity and become

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Table II Group II

	Initial cardiac catheterization				Repeat cardiac catheterization					
Case No	*Age in years*	*RVS (mm Hg)*	*PA S/D (mm Hg)*	*PA–RV Peak systolic gradient (mm Hg)*	*Age in years*	*RVS (mm Hg)*	*PA S/D (mm Hg)*	*PA–RV peak systolic gradient (mm Hg)*	*PFO*	*Surgery after second catheter*
1	5	4ı	22/10	23	10	45	°2/10	23	0	0
2	4	60	°4/10	36	8	60	18/8	4°	+	0
3	3	45	20/15	°5	8	60	21/10	39	0	0
4	4	54	15/8	39	8	55	12/8	43	0	+
5	5	56	25/15	31	15	60	18/12	42	0	0
6	5	60	18/10	4	17	60	18/10	42	0	0
7	4	44	15/10	29	11	4ı	15/8	30	+	0
8	6	43	16/10	27	11	90	20/10	70	0	+
9	10	45	20/12	25	19	45	20/10	25	0	0
10	11	55	20/10	35	16	55	0/12	35	0	0
11	2	ˬ4	1°/5	4°	11	130	°0/11	110	0	+
12	10	42	22/12	20	13	46	20/10	26	0	0
13	6	47	21/11	26	11	48	°1/14	27	0	0
14	2	60	20/10	40	5 5	120	25/12	95	0	+
15	3 5	60	18/6	42	7	60	17/8	43	0	0
16	5	50	20/10	30	11	50	°0/12	30	0	0
17	3	46	16/8	30	8	46	16/9	30	0	0
18	1 ˬ	55	18/10	37	5	55	1 /10	38	0	0
19	3	7ˀ	20/10	52	10	98	22/15	6	0	+
20	13	70	16 8	54	17	130	15/7	115	0	0
21	2	74	18/10	56	9	74	18/12	ˬ6	0	+
2ˀ	14	75	15/10	60	20	210	20/14	190	0	0
23	2	64	18/10	4ˬ	4 ˬ	85	°5/10	60	+	+
24	5	79	18/1°	61	1°	50	ˍ0/15	30	0	0
25	4	84	18/10	66	7	84	18/10	66	+	0
26	°	86	°6/13	60	5	115	18/9	97	+	+
27	2	70	ˍ0/10	50	3 5	106	°6/10	80	0	+
28	3	94	19/1	75	4 5	94	20/10	74	+	+
29	°	8ˀ	ˬ0/11	6ˀ	5	62	2°/10	40	+	0
30	7	100	°0/12	80	16	100	2ˀ/15	78	0	+
31	1.5	10	15/10	90	5 5	200	°0/12	180	0	+

PA = pulm nary artery PFO = p t nt f r m n o le RV = right e tri le
RVS = right ventricul sy t lic S/D = systoli / dia t lic

measurement would decrease somewhat the value of our hemodynamic data but this information was most difficult to obtain in patients under one year of age at the time when these infants were initially studied

Incidence of patent foramen ovale Tables I and II show the incidence of both foramen ovale in Groups I and II Patent foramen ovale was present in 26 out of 37 patients in Group I compared with seven out of 31 patients in Group II It is known that patent foramen ovale is found more frequently in the first year of life than in the older patients and this might be a factor responsible for this Of course there is always a possibility that a patent foramen ovale was unrecognized at cardiac catheterization No shunting was noted across the foramen ovale and these were functionally intact

Surgery Twenty five of the 37 patients in Group I required surgical pulmonary valvotomy after the second study In contrast only 12 of the 31 patients in Group II required a valvotomy These figures indicate that surgery was required more often in Group I than in Group II

Discussion

The fate of patients with isolated valvular pulmonic stenosis of varying severity has been discussed in the literature and the natural history outlined Follow up information on patients with

Table I Group I

Case No	Initial cardiac catheterization: Age in months	RVS (mm Hg)	PA S/D (mm Hg)	PA–RV Peak systolic gradient (mm Hg)	Repeat cardiac catheterization: Age in years	RVS (mm Hg)	PA S/D (mm Hg)	PA–RV Peak systolic gradient (mm Hg)	PFO	Surgery after second catheter
1	2	40	20/10	20	8	45	22/12	23	+	0
2	2	60	21/12	39	7	42	20/10	22	+	0
3	3	47	20/10	27	7	60	20/10	40	+	0
4	10	45	22/10	23	4	70	20/6	50	+	0
5	12	54	16/6	38	2.5	60	20/9	40	0	+
6	11	40	15/8	25	9	86	16/7	70	0	+
7	0.5	42	15/10	27	9	65	18/9	47	+	0
8	8	58	25/13	33	5	77	19/9	58	+	+
9	11	45	20/10	25	5	80	23/7	57	0	+
10	3.5	56	20/6	36	4	90	26/10	64	0	0
11	7	50	20/10	30	4.5	86	16/10	70	+	+
12	1	45	18/12	27	4	97	25/12	72	+	+
13	2	54	22/10	32	4.5	76	28/14	48	+	0
14	3	66	22/5	34	3.5	60	24/8	36	+	0
15	2	50	20/10	30	3	96	20/8	76	0	+
16	12	70	25/13	45	7	80	24/14	56	+	0
17	6.5	90	30/15	60	2	115	15/5	100	0	+
18	2	65	34/15	31	3.5	75	18/9	57	0	+
19	5.5	70	25/11	45	4	100	20/10	80	+	+
20	7	72	20/10	52	2.5	85	11/4	74	+	+
21	3	90	24/14	66	3.5	115	28/14	87	+	+
22	12	62	14/8	48	11	100	17/9	83	+	+
23	5.5	64	21/13	43	6	105	20/10	85	0	+
24	2	78	23/10	55	2	84	20/8	64	+	+
25	11	87	30/15	57	2.5	105	25/8	80	0	+
26	2	72	23/11	49	2	140	15/5	125	+	+
27	12	72	22/11	50	7	55	20/10	30	0	0
28	12	62	20/12	42	5	108	20/10	88	0	+
29	3	88	10/3	78	2	102	10/3	92	+	+
30	6	78	14/6	64	4.5	104	20/9	84	+	+
31	4	62	26/12	36	4.5	67	21/7	46	+	0
32	12	68	20/10	48	7	135	20/10	115	+	+
33	1	110	10/5	100	1.5	210	10/4	200	+	+
34	5	104	14/8	90	2	220	10/5	210	+	+
35	1	108	25/10	83	3	112	17/7	95	+	+
36	4.5	106	26/14	80	3	148	16/6	132	+	+
37	8	114	20/10	94	3.5	142	10/5	132	+	+

PA = pulmonary artery PFO = patent foramen ovale RV = right ventricle
RVS = right ventricular systolic S/D = systolic / diastolic

moderate or severe as they grow older Those with moderate stenosis can become more severe as the years go by Also, patients with severe stenosis can have a further increase in their right ventricular pressure Tables II and III also demonstrate the right ventricular pressure in Group II at the two studies There were 18 patients who at initial study, were considered mild and there were 16 patients who had remained mild at repeat study – demonstrating that mild stenosis in this group had not changed significantly in severity – unlike the first group In the group with moderate stenosis there were 12 patients at the initial study and eight at repeat study Six of these patients had now become severe The number for severe stenosis had increased from one to seven mainly because of increasing severity of moderate stenosis Valve areas were not calculated because cardiac output was not measured in these patients We realize that lack of cardiac output

strated that surgery is much more often required in children in Group I than in Group II The disease seems to be more progressive and unpredictable in Group I than in Group II where the severity seems to be more or less established We would therefore give a more guarded prognosis for infants and children under one year of age even with a mild degree of pulmonic stenosis regarding future need for surgery Unlike Engle Ito and Goldberg s patients none of our patients in the present study developed subacute bacterial endocarditis Because of this selective nature of our group none of our patients were symptomatic or were in cardiac failure We did have such a group of patients but they were operated upon immediately and therefore did not fulfill the criteria for our current study We agree with the others that no restrictions in activities are necessary in mild stenosis

We conclude that mild stenosis as seen in infants under one year of age can become severe at a later date Mild stenosis seen after one year of age is unlikely to become severe Moderate and severe lesions as seen in those under one year of age or over one year of age can both be progressive In general mild and moderate valvular pulmonic stenosis has a good prognosis without undue complications

Summary

Sixty-eight patients with isolated valvular pulmonic stenosis with intact ventricular septum diagnosed by cardiac catheterization underwent a repeat study one to twelve years later which documented the progression of the lesion These 68 patients were classified into two groups according to age Group I comprised 37 patients who were less than one year of age at the initial study and Group II comprised 31 patients who were older than one year of age at the time of the initial study These 68 patients were divided into three groups according to their systolic right ventricular pressure and classified as mild moderate or severe Increasing severity of the lesion was noted much more frequently in Group I even with patients who were noted to have mild stenosis at initial cardiac catheterization This was not as marked in Group II The incidence of patent foramen ovale was noted to be much higher in Group I as compared with Group II A much greater number of patients required surgery after repeat cardiac catheterization in Group I as compared with Group II Our data indicate that mild cases of pulmonic stenosis in Group I can become severe at a later date whereas this was less likely in Group II Those with moderate and severe stenosis can remain the same or become more severe as age advances in both groups

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Table III Right ventricular pressure—Group I and II

	Group I		Group II	
	Initial study	Repeat study	Initial study	Repeat study
Mild (under 60 mm Hg)	15	6	18	16
Moderate (60 100 mm. Hg)	17	17	12	8
Severe (over 100 mm Hg)	5	14	1	7
Total	37	37	31	31

this lesion initially studied under one year of age is not well documented It has also been clearly stated that mild and moderate degrees of pulmonic stenosis have a good prognosis In the older age group, survival beyond the age of 70 has been reported by a number of authors [1 3] Tinker and co workers[4] described 39 patients with mild to moderate stenosis and 36 patients with severe stenosis No deterioration or deaths were noted in the mild to moderate group In contrast in the severe group effort tolerance deteriorated in six, two died four showed increasing right ventricular hypertrophy and four developed isolated progressive T wave changes Baritt[5] also found no evidence of deterioration in similar groups of patients Wood[6], in 1956, reported that some of his patients who had moderate valvular pulmonic stenosis were first class athletes Johnson and co workers[7], in 1972, described 21 patients with valvular pulmonic stenosis in adults with a follow up of an average of 50 years Of these 21, 12 were mild seven moderate and two severe Of the 21 at follow up, one had died of trauma and the other 20 were alive and well None had developed endocarditis or cardiac symptoms After describing the benign course Johnson and co workers[7] recommended that surgical correction was indicated only in the presence of symptoms or complications of pulmonic stenosis Engle Ito and Goldberg[8] indicated that pulmonic stenosis could become progressively more severe with growth of a young child but suggested that it was impossible to predict which one would follow that course

Their findings agreed with the other authors — that if the obstruction had been mild through adolescence into adult life then this cardiac dysfunction was not going to be significant They also mentioned that physical activity need not be curtailed in cases with mild stenosis when surgery was not indicated Seven of their patients developed bacterial endocarditis, and they recommended proper prophylaxis for prevention of bacterial endocarditis in all groups of patients with isolated pulmonic stenosis In their opinion, surgery was indicated in severe lesions regardless of age and certainly if they were in heart failure. Mustard, Jain and Trusler[9], in 1968 described 26 infants with severe pulmonic stenosis in the first year of life They felt that this lesion may be extremely dangerous and recommended surgical therapy Gersony and co workers[10] and Gibson and co workers[11] concurred with Mustard Jain and Trusler s[9] findings and indicated that this group of infants under one year of age with severe stenosis behaved differently from older patients with similar problems because of the severe and progressive nature of the disease Howitt[1] studied the hemodynamic effect of exercise on patients with pulmonic stenosis and noted that all the patients with severe stenosis had impaired cardiac output response to effort In contrast, mild and moderate stenosis had a normal output response They mentioned that patients with severe stenosis may have severe impairment of effort tolerance and may develop cardiac failure His group dealt with an average age of 32 8 years for severe lesions and 35 7 years for moderate and severe cases with normal response Howitt s findings were similar to those described by Ikkos Johnson, and Linderholm[13] who also found that in severe cases cardiac output and other parameters were below normal, and in less severe situations this approached more or less the normal state Dow and co workers[14] mentioned that there was no indication that a failure to increase cardiac output occurred in those patients with high right ventricular pressures Our findings indicate that isolated valvular pulmonic stenosis even of mild severity can become of surgical importance at a future date in children under one year of age at the time of initial study We feel that if the lesion remains mild after one year of age it is unlikely to progress significantly, as shown in our Group II This is in agreement with the other authors that we have mentioned earlier In our opinion moderate and severe lesions can increase in severity in both the under one year and over one year age groups at follow up We agree with other authors that surgery is probably indicated in this group We have also demon

Table I Per cent smoking cigarettes by age and sex Framingham Study Exams 1 and 10

Age	Men		Women	
	Exam 1	*Exam 10*	*Exam 1*	*Exam 10*
All ages	61 0	37 1	40 2	31 0
29 33	62 8	43 8	51 1	43 0
34 37	71 5	48 0	56 6	48 5
38-41	67.2	45.2	48 8	37.2
42-45	58 0	32 4	38 0	29.8
46-49	56 1	29 9	28 1	20 0
50-53	58 9	32 1	28 7	18 7
54 57	43 6	18 8	23 4	12 4
58-62	48.3	18 6	15 0	6 0

Persons must take both Exams. 1 and 10 to be incl ded Age is at Exam. 1 and defines ge- pecific c horts followed for 18 years

Table II Per cent of men and women not smoking cigarettes after 18 years by original smoking status Framingham Study*

Amount smoked at Exam 1 (No of cigarettes/ day)	Men		Women	
	No at entry	*Not smoking at Exam 10 (%)*	*No at entry*	*Not smoking at Exam 10 (%)*
0	599	95 7	1226	97 0
1 10	165	58 2	417	39.3
11 19	89	41 6	139	18 0
20	393	38.2	208	13 5
21-39	188	38 3	41	14 6
40+	98	35 7	18	5 6

*Includes only persons wh took Exam. 10

smoking at entry serving as a reference group Statements of statistical significance are made at a 5 per cent level.

It is of course difficult to decide when a person has quit smoking cigarettes and the criteria followed early in the study are not well defined On later examinations a person who had smoked for more than a year in the last 2 years was classified as a smoker whatever his immediate smoking behavior The relapse rate for those classified as quitting is low enough throughout the study to suggest that the criteria for quitting must always have excluded persons who were only beginning to try Only about 20 per cent of the men who reported that they had quit at entry ever reported smoking cigarettes again and nearly half of those who resumed smoking smoked very little or only intermittently after resumption

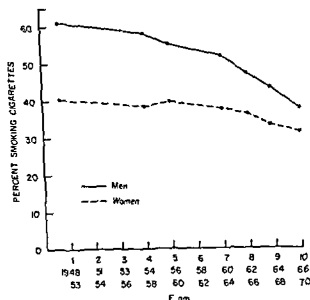


Fig 1 Per cent of men and women smoking cigarettes on examination Framingham Study Exams 1 to 10

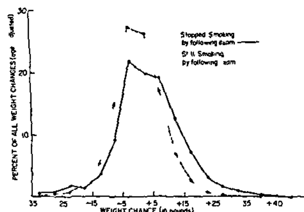


Fig 2 Weight change according to change in smoking habits in men under 65 years of age smoking cigarettes on examination Framingham Study Exams 1 to 10

Results

Changes in smoking habits Trends from 1948 to 1953 when the initial examination was performed to the tenth biennial examination in 1966 to 1970 are shown for men and women in Fig 1 Only persons taking both Exams 1 and 10 are included At entry 61 per cent of the men and 40 per cent of the women smoked cigarettes Eighteen years later only 37 per cent of the men and 31 per cent of the women were still smoking

Changes associated with quitting cigarette smoking The Framingham Study

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William B Kannel, M D
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Since 1948, when the Framingham Study began, there has been a substantial change in cigarette smoking habits in the United States One of its features—perhaps the most striking one—has been the substantial number of middle aged men who have quit cigarette smoking[1,2] Presumably this has led to changes in medically related characteristics and in disease The Framingham Study, which has had a general population under continuous observation during this period, provides an opportunity to assess the changes that have occurred

Methods

The Framingham Study cohort when it first came under observation was 29 to 62 years old The initial study population came from a sample of adults resident in the town of Framingham Mass, and consisted of 5,209 men and women They received a thorough standardized cardiovascular examination at entry which also elicited a large amount of information about their habits their physical characteristics, their blood chemistry, and the like Similar examinations were repeated every 2 years This was supplemented by information on cardiovascular illness and death obtained from hospitals and other extra clinic sources[3]

Details with respect to laboratory methods and clinical criteria are available elsewhere[4] Histories of cigarette smoking were obtained on every examination except Exam 6 however, information from the first three examinations was coded to represent usage at Exam 1, leaving Exams 2 and 3 uncoded (More than half of those coded to Exam 1 actually derived from Exam 1 the bulk of the remainder from Exam 2) Unless otherwise specified "smoking means smoking cigarettes

In previous reports from the Framingham Study, ' quitting ' was defined retrospectively by a history of previous smoking habits obtained at entry to the study Some data in that form are presented in this report but this is supplemented for the first time by information on people who were smoking when they first came under observation and who while they were still under observation quit smoking Weight, blood pressure, vital capacity, drinking habits, and so on, were measured while they were still smoking and again after they quit What happened concurrently to people smoking at entry who continued to smoke is also available from the routine re examination of the cohort

Changes in characteristics are examined in two ways (1) short term changes occurring in the interval between the last examination while smoking and the following examination that is the first examination after quitting, and (2) long term changes (between Exams 4 and 10) for persons smoking at entry but quitting by Exam 4 Age specific means for the characteristics were calculated for the age groups 35 to 44 45 to 54 and 55 years and over (age at Exam 4) These means provided the basis for age adjustment Comparisons are made between those who quit and those continuing to smoke with those not

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Table I Per cent smoking cigarettes by age and sex Framingham Study Exams 1 and 10*

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	Exam. 1	Exam 10	Exam 1	Exam 10
All ages	61 0	37 1	40 2	31 0
29 33	6? 8	43 8	51 1	43 0
34 37	71 5	48 0	56 6	48.5
38-41	67.2	45 2	48 8	37.2
42-45	58 0	3? 4	38 0	29 8
46-49	56 1	29 9	?8 1	20 0
50-53	58 9	3? 1	8?	18 7
54-57	43 6	18.8	23 4	12 4
58-62	48 3	18 6	15 0	6 0

Persons must take both Exams. 1 and 10 to be included Age is t E m 1 and d fines age-specific coh rts followed for 18 y ars

Table II Per cent of men and women not smoking cigarettes after 18 years by original smoking status Framingham Study*

Amount smoked at Exam 1 (No of cigarettes/ day)	Men		Women	
	No at entry	Not smoking at Exam 10 (%)	No at entry	Not smoking at Exam 10 (%)
0	599	95 7	1??6	97 0
1 10	165	58 2	417	39.3
11 19	89	41 6	139	18 0
20	393	?8.2	208	13.5
21 39	188	38.3	41	14 6
40+	98	35 7	18	5 6

I cludes only persons who took E am. 10

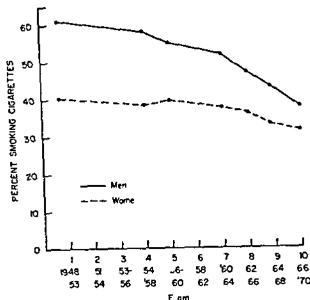
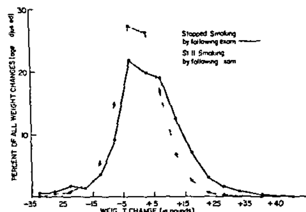


Fig 1 Per cent of men and women smoking cigarettes on examination Framingham Study Exams 1 to 10



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It is of course difficult to decide when a person has quit smoking cigarettes and the criteria followed early in the study are not well defined On later examinations a person who had smoked for more than a year in the last 2 years was classified as a smoker whatever his immediate smoking behavior The relapse rate for those classified as quitting is low enough throughout the study to suggest that the criteria for quitting must always have excluded persons who were only beginning to try Only about 20 per cent of the men who reported that they had quit at entry ever reported smoking cigarettes again and nearly half of those who resumed smoking smoked very little or only intermittently after resumption

Results

Changes in smoking habits Trends from 1948 to 1953 when the initial examination was performed to the tenth biennial examination in 1966 to 1970 are shown for men and women in Fig 1 Only persons taking both Exams 1 and 10 are included At entry 61 per cent of the men and 40 per cent of the women smoked cigarettes Eighteen years later only 37 per cent of the men and 31 per cent of the women were still smoking

Table III Mean values of specified characteristics at entry by smoking status Framingham Study*

Sex characteristic	No of cigarettes/day									
	None				Cigarette smoker					
	Total	Never	Quit	Cigar pipe	Total	1 10	11 19	20	21-39	40+
Men number	803	277	215	311	1 498	254	139	608	314	183
Age adjusted mean values										
Systolic blood pressure (mm Hg)	138 1	139 4	137 8	138 0	136 1	138 1	133 9	134 8	136 8	138 1
Diastolic blood pressure (mm Hg)	87 8	87 5	87 4	88 3	85 4	86 8	83 5	84 9	85 6	86 7
Vital capacity (L)	381 2	382 4	382 4	379 4	371 4	372 4	372 3	373 7	372 5	359 6
Alcohol (oz /mo)	17 4	10 0	20 7	21 7	27 5	23 4	18 3	24 1	30 7	45 8
Weight (lb)	172 9	173 4	171 7	173.2	164 7	165 0	160 5	162 9	166 4	170 2
Uric acid (mg /100 ml)	5 3	5 2	5 3	5 2	5 0	5 2	4 9	5 0	5 1	5 2
Serum cholesterol (mg /100 ml)	224 0	222 0	230 5	221 3	228 5	225 4	226 1	228 6	229 6	232 5
Blood sugar (mg /100 ml)	83 4	84 1	82 7	83 2	82 4	81 6	82 9	82 5	81 6	83 8
Women number	1 634	1543	91	–	1 174	580	182	313	75	24
Age adjusted mean values										
Systolic blood pressure (mm Hg)	138 5	138 7	135 6	–	134 5	133 9	134 4	134 7	131 5	154 9
Diastolic blood pressure (mm Hg)	85 6	85 6	84 6	–	83 5	83 5	82 3	83 4	83 7	92 5
Vital capacity (L)	255.8	254 7	274.9	–	262.9	264 0	263 6	262 2	260 6	244 8
Alcohol (oz /mo)	4 4	4 1	9 2	–	10 5	8 4	11 0	11 6	17 7	19 6
Weight (lb)	143 7	144 0	139 1	–	138 1	139 4	133 2	138 1	139 2	144 4
Uric acid (mg /100 ml)	4 0	4 0	4 1	–	4 0	4 0	4 0	4 0	4 5	4 3
Serum cholesterol (mg /100 ml)	227 5	227 6	226 2	–	230 6	226 9	235 4	234 1	240 8	209 8
Blood sugar (mg /100 ml)	82 8	83 0	79 8	–	81 2	82 0	81 2	79 9	80 9	77 4

*Mean values for the age groups 29-44 45-54 and 55 62 were weighted 12/22 7/22 and 3/22 respectively to yield age adjusted mean values

Decreases were fairly continuous during those 18 years beginning as early as the second examination (1951 to 1954) with an accelerated rate of decline especially apparent in men beginning after Exam 7 (1960 to 1964) Additional details of these changes are available elsewhere [5]

Table I compares the per cent smoking at Exam 1 with the per cent smoking at Exam 10 Decreases were observed for all age groups By Exam 10 men had dropped to about the Exam 1 smoking levels of women Women smokers were more persistent in retaining their original smoking habits although even for them small decreases were observed for every age group

The more a person smoked at entry the less likely he was to be a nonsmoker 18 years later (Table II) Quit rates for women were lower than those for men in all smoking categories So few Framingham women quit since the study began that their experience is not analyzed in this report

Characteristics by smoking habit at entry At entry body weight varied according to smoking habit For men the difference between cigarette smokers and nonsmokers was 8 pounds (Table III) Nonsmokers include those who never smoked those who had quit, and those smoking cigars or pipes There is little difference in their weights Smokers weights varied with the amount smoked but no matter how many cigarettes were smoked per day, the average weight was less than that for nonsmokers The leanest smokers were those smoking 11 to 19 cigarettes per day Men smoking more than this weighed more, their weight being greater the more they smoked Men smoking 40 or more cigarettes per day weighed nearly as much as nonsmokers Data for women were very similar Thus, while weight is clearly related to the fact of smoking and to the amount smoked the association is nonlinear and therefore cannot be satisfactorily represented by a correlation coefficient or linear regression

In addition to weight only two other of the characteristics listed in Table III were found to differ between smokers and nonsmokers at entry—alcohol and vital capacity Persons who never smoked used little alcohol, on the average, while men or women who smoked used more, the amount being greater the more cigarettes smoked Vital capacity is lower among men smoking ciga

Table IV Age adjusted mean levels at entry of selected characteristics for cigarette smokers according to subsequent smoking history Men Framingham Study

Characteristic	*Mean level at entry**			
	Men smoking 1 10 cigarettes/day at entry		*Men smoking 20 cigarettes/day at entry*	
	Still smoking at Exam 4	*Not smoking at Exam 4*	*Still smoking at Exam 4*	*Not smoking at Exam 4*
Systolic blood pressure (mm Hg)	137.3	136 0	134.5	131 1
Diastolic blood pressure (mm Hg)	86 7	85 3	84 8	83.2
Vital capacity (L)	367.8	382 3	375.5	382.2
Alcohol (oz /mo)	23 4	21.8	24.5	23 6
Weight (lb)	164 1	168 2	162 8	162 8
Uric acid (mg /100 ml.)	5 2	5.2	5 0	5 0
Serum cholesterol (mg / 100 ml)	223 6	225 5	228 8	228 8
Blood glucose (mg /100 ml.)	79 4	93 6	79 1	87.9

Age- djusted m ans are unweighted averages of th age-specific m ans

rettes than those not smoking For women the difference in vital capacity is in the opposite direction Both contrasts are statistically significant if relatively small Persons of either sex smoking 40 or more cigarettes per day have distinctly lower vital capacities than others but few women smoked 40 or more cigarettes per day

Characteristics of men who later quit Since so few women have quit smoking all the subsequent analysis is confined to men

It seems likely that men who quit smoking are different from persons who continue smoking What is not clear is whether the differences are such as to influence subsequent morbidity and mortality rates Without a clinical trial involving randomization and the other usual safeguards of such trials it is impossible to conclusively resolve such an issue but it is possible to look at some relevant characteristics of smokers measured while they were still smoking and compare those smokers who subsequently quit with those who continued smoking (Table IV) Data are presented separately for men smoking one to 10 cigarettes per day and exactly 20 cigarettes per day at entry These two groups account for the bulk of those subsequently quitting

When these comparisons are made only minor differences in general are noted There were only trivial and not statistically significant differences between those who later quit and those who continued smoking with respect to their entry levels for blood pressure vital capacity alcohol consumption weight uric acid or serum cholesterol There was one exception Men who quit had a higher average blood glucose level before quitting than men who continued smoking Most of the difference is accounted for by an excess number of diabetic subjects among smokers who quit smoking This presumably indicates that ill health (in this instance diabetes) is an incentive to stop smoking

Short term changes after quitting Under observation men under age 65 who quit smoking gained a small amount of weight immediately (3 8 pounds on the average) (Table V) If they were still not smoking at the next examination their weight remained fixed at the new level (For this subgroup off cigarettes for two full examinations the average initial gain was 5 1 pounds followed by a trivial gain—0 3 pounds—in the next 2 years) While there is a slight tendency toward weight gain (about half a pound) in men whose smoking habits remained unchanged from one examination to the next this was of course significantly less than the weight increase for those who quit Persons who resumed smoking lost about a pound after resumption

Illness particularly the onset of clinical cardiovascular disease may be a powerful incentive to stopping smoking and is also associated with weight changes The average weight gain

Table V Changes in weight, systolic blood pressure, and serum cholesterol levels by change in smoking habits Framingham Study, men under age 65 years*

Change in smoking habits from one exam to next	*No* †	*Average change in characteristic*			
		Weight (lb)‡		*Systolic blood pressure (mm Hg)*	*Serum cholesterol (mg/100 ml)*
Smoking to nonsmoking	541	3 8	(2 3)	1 6	0 2
Continued smoking	4 078	0 3	(0 1)	0 7	−0 2
Nonsmoking to smoking	246	−0 9	(−0 8)	0 6	1 9
Continued not smoking	3 120	0 5	(0 1)	0 7	0 3

*Smoking histories are available at Exams 1 4 5 7 8 9 and 10 Only reports of current smoking practices are considered and are compared with measurements on the same pair of examinations The intervals are those between exams with smoking histories
†Number of changes, not number of persons
‡Parenthetical entries are for men free of cardiovascular disease on the first examination considered

after quitting is less if such persons are omitted but the difference is trivial

The average difference in weight change between those who quit and those who continued smoking cigarettes is not accounted for by a few men with very large weight gains but arises from the fact that proportionately fewer among those who quit lost weight and more among them gained at least 10 pounds (Fig 2)

One would anticipate that the greater weight increase in smokers who quit relative to those continuing to smoke would be associated with relatively greater increases in blood pressure and serum cholesterol In fact the difference in trends for these two characteristics is trivial and not statistically significant (Table V)

Table VI considers changes for a number of characteristics in men who were smoking either one to 10 or 20 cigarettes per day at Exam 1 These men are divided into two groups according as they were or were not still smoking at Exam 4 Short term changes for those who quit are contrasted with short term changes for those still smoking at Exam 4 in the upper half of the table These changes are compared with concurrent changes for those who continued to smoke Both groups may be compared with those men who were not smoking at entry

For two characteristics—weight and vital capacity—men who quit smoking by Exam 4 had statistically significant differences in trends from men still smoking at Exam 4 The weight increase from Exams 1 to 4 was greater for men who quit than for men who continued smoking the difference being statistically significant for men smoking 20 cigarettes per day at entry

Men smoking 20 cigarettes per day who quit also had a statistically significant and substantially greater decrease in vital capacity between Exams 1 and 4 than did those still smoking This presumably implies that respiratory distress was one of the motives for quitting

Significant differences in short term trends for those quitting and those continuing to smoke were not evident for alcohol consumption uric acid serum cholesterol, or blood sugar

Long term changes after quitting Long term changes after quitting are shown for the 12 years between Exams 4 and 10 in the lower half of Table VI These may be contrasted with the initial short term changes already discussed

There was a greater long term decline in vital capacity for those who continued smoking than for those smoking the same amount who quit For men smoking 20 cigarettes per day at entry the difference in trends was statistically significant The long term vital capacity trends of those who quit approached the concurrent experience of men who were not smoking at entry

Men who continued smoking had a greater long term drop in serum cholesterol levels than those who quit but this difference was not statistically significant Men who continued to smoke also had a slightly smaller long term rise in blood pressure but, again, the difference was not statistically significant After the initial weight changes the long term changes in weight for men who quit and men who continued to smoke cannot be distinguished

In brief, the only statistically significant difference in long term trends among the variables considered is the greater drop in vital capacity for

Table VI Change in smoking habits in men between Exams 1 and 4 and concurrent and subsequent changes in certain other characteristics Framingham Study

Characteristic	Not smoking at entry	1 10 cigarettes/day at entry		20 cigarettes/day at entry	
		Quit at Exam 4	*Still smoking at Exam 4*†	*Quit at Exam 4*	*Still smoking at Exam 4*†
Increase from Exams 1 to 4	(714)‡	(51)	(15?)	(58)	(464)
Systolic blood pressure (mm Hg)	–4 00	–4.98	–3 08	0.97	–1 79
Diastolic blood pressure (mm Hg)	–2 88	–3 04	–2 63	–0 16	–1.88
Vital capacity (L.)	–9 42	–18 63	–11 64	–21 48	10.82
Alcohol (oz /mo)	2 07	–0 22	2.37	2 79	1.25
Weight (lb)	2.53	3 43	1.36	7 ?8	2.70
Uric acid (mg /100 ml)	–0 ?0	–0 31	–0 20	–0.29	–0 06
Serum cholesterol (mg /100 ml)§	6 38	5.32	12.18	6 43	7.53
Blood glucose (mg /100 ml.)	0 21	–2 70	0 77	8.54	1 97
Increase from Exams 4 to 10	(564)	(43)	(105)	(39)	(348)
Systolic blood pressure (mm Hg)	7 66	10 12	7.57	9.26	6.83
Diastolic blood pressure (mm. Hg)	–1 74	–1 72	–0 07	–0 79	–0.92
Vital capacity (L.)	–41 16	–40 47	–45 11	–41 76	–55.88
Alcohol (oz /ml)‖	1.92	3.27	7.57	3.88	4.21
Weight (lb)	–1.50	3 14	1.20	0 03	0 19
Uric acid (mg /100 ml)	N.A	N.A	N.A	N.A.	N.A.
Serum cholesterol (mg /100 ml.)	–7 47	–9 32	–17 78	–5 48	–12.27
Blood glucose (mg /100 ml)¶	10 39	2 83	5 19	2.16	7 66

Adjusted to the age-distribution of men smoking 1 10 cigar ttes who quit d who took Exam 4 (10)
†Adjusted to the ag -distribut on f men moki g the sam am nt wh quit
‡Parenthetical ntries are th number of men in e ch gr p
§Exams 2 and 4
‖Exams. 4 and 7
¶Exams. 4 and 9

men smoking 20 cigarettes per day at entry who continued to smoke

Discussion

While there is a considerable literature on the characteristics of men according to their smoking histories there is very little information on what happened to men who quit smoking while under observation Presumably such information is available in the files of various prospective studies but the subject seems to have excited little analytical interest

An exception is the Normative Aging Study which has recently published data on subjects measured 5 years apart When the data for 214 continuing cigarette smokers are contrasted with data for 104 quitters the difference in weight gain was 4 2 pounds. This is very similar to the Framingham findings Findings with respect to blood pressure changes however differed somewhat[1] The Normative Aging Study reported continuing smokers had on the average no change in systolic blood pressure in 5 years but men who quit had slightly higher systolic levels after quitting (3 6 mm Hg) While this is a trivial difference and is probably of marginal statistical significance it was noted that there was a greater blood pressure gain in each weight group among quitters than those continuing to smoke

The comparable data for Framingham would be those given in Table V for changes between Exams 1 and 4 These show no difference in blood pressure trends for those who continued to smoke and those who quit despite a greater weight increase in those who quit Unfortunately strict comparability cannot be achieved since the Normative Aging Study did not include men if their initial blood pressure was greater than 140/90 whereas there were no blood pressure exclusions in the Framingham Study

What is most striking in the Framingham data is how little difference there is between those who quit and those who continued smoking either in their characteristics while still smoking or with respect to changes in these characteristics after stopping Of the characteristics examined only

two stand out—weight and vital capacity A slightly greater short term weight change and a smaller long term decline in vital capacity among those who quit than among those who continued smoking were the chief findings Only for men smoking more than 10 cigarettes per day were these differences statistically significant No significant changes in blood pressure or serum cholesterol levels were found to be associated with quitting cigarette smoking

Information with respect to women smokers and with respect to men smoking more than a pack a day was too scanty for analysis, and it is conceivable that the effect of quitting is different in these groups than in the groups available for analysis Men smoking a pack or less a day constitute the bulk of those who quit cigarette smoking and are consequently the group of major public health interest In this group the impact of quitting on the major cardiovascular risk factors appears to be trivial so that the cardiovascular advantage of quitting cigarette smoking should be straightforward

Summary

During the first 18 years of the Framingham Study there was a substantial decrease (39 per cent) in the number of men smoking cigarettes and a moderate decrease (22 per cent) in the number of women smoking cigarettes Except for a greater tendency of diabetic patients to quit smoking there were no significant differences at baseline between smokers who quit and smokers who continued smoking After quitting there was a short term rise in weight for men This rise led only to trivial changes in blood pressure and serum cholesterol levels There was a beneficial impact on long term vital capacity trends from quitting smoking

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Diagnostic accuracy of an ultrasonic multiple transducer cardiac imaging system

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In order to simplify visualization of the human heart in vivo without radiation hazard or invasion of the body an ultrasonic imaging system has been developed by Dr Nicholas Bom and Prof Paul Hugenholtz of Rotterdam The Netherlands A prototype unit was placed in the Stanford University Non Invasive Laboratory as part of a cooperative study by four centers to evaluate the unit s ability to visualize intracardiac structures The results of this cooperative study are reported elsewhere The diagnostic accuracy of this system was evaluated in the clinical setting using adult patients and this is a report of the initial findings

Methods

The technical aspects of the multiple transducer system have been described in detail in the past Basically the unit consists of 20 small ultrasonic transducers arranged in a linear array and housed in a single unit 8 cm in length Each transducer is pulsed for 1 μsec and then acts as a sound receiver for the subsequent 230 μsec corresponding to 16 cm of tissue depth After this time interval the next transducer is pulsed and each subsequent transducer is pulsed and acts as its own receiver until all 20 units have been used at which time this cycle is repeated This time sequence results in a two dimensional image of 8 by 16 cm appearing at a rate of 150 complete frames per second To improve resolution two frames may be interlaced giving a 40 line display at 75 frames per second The path of each sound beam is displayed on an oscilloscope face as a horizontal line with a bright electronic dot corresponding to the intersection of the sound beam and each interface of tissue having different acoustic impedance (density × velocity) (Fig 1) This two-dimensional image shows movement in real time and may be recorded with a video tape system or moving picture photography

The transducer array was placed on the chest wall with a gel used to insure airless contact of the transducer and skin The transducer first was placed along a path from the cardiac apex to the angle of Louis By watching the oscilloscope it is possible to recognize a view of the heart roughly corresponding to a lateral angiographic picture The transducer is placed high or low on the chest wall to show the area of the aortic root and mitral valve preferentially It was often necessary to rotate the transducer array in a clockwise or counter clockwise direction about an axis taken from the center of the transducer face to the center of the transducer back perpendicular to the chest wall This maneuver permitted one to locate the plane of the left ventricular outflow tract Then it was possible to pivot the transducer about an axis from the top to the bottom of the transducer face parallel to the chest wall so that medial or lateral portions of the heart were visualized With these three transducer maneuvers one may image a large portion of the heart and develop an integrated mental image of the cardiac structures

Eighty consecutive patients showing good quality records by conventional echocardiography were examined with the new ultrasonic

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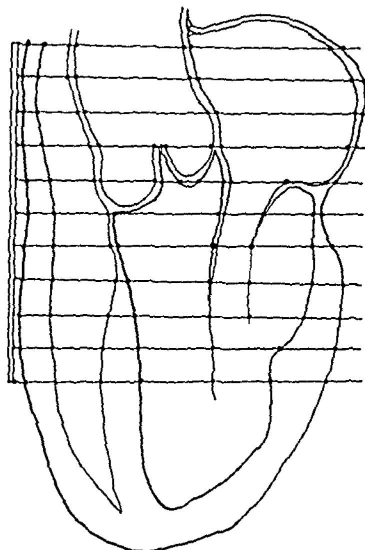


Fig 1 Diagram of method of cardiac image production by a linear array (left) of ultrasonic transducers placed on the chest wall over the heart Each horizontal line represents a single sound beam The intersection of each sound beam and echo producing surface is indicated by a dot on the oscillo scope face Rapid switching activates each transducer sequen tially and produces a two dimensional image of a single slice through the heart Note that the 8 cm long transducer array does not encounter the full length of the adult heart rou tinely

unit These examinations were recorded on video tape with only a coded number for patient iden tification At a later time after all 80 patients had been examined, two observers who were familiar with the technique reviewed the records At this point a decision was made regarding the probable diagnosis from the anatomic and physiologic patterns observed on the video tape records These diagnoses were recorded and compared with the information available from hemody namic and angiographic studies

Results

The results of this study are summarized in Table I Thirty three of the 80 patients studied had a final diagnosis of (1) coronary artery disease (2) left ventricular volume overload (pre dominately due to mitral or aortic regurgitation), or (3) normal angiographic and hemodynamic study These patients could not be consistently separated into these three groups by the patterns seen with the multiple transducer system Quan titative studies of left ventricular volume and change in volume during the cardiac cycle were not done in these patients All 15 patients with mitral valve prolapse were recognized with the multiple transducer system and one patient was falsely diagnosed as having this condition due to apparently excessive motion of the anterior mitral leaflet Mitral stenosis was properly diag nosed in all 13 patients and two patients without this condition presented false positive diagnoses This was due to the presence of a large left atrium and apparently slow ventricular diastolic filling in the presence of multiple echoes from the valve area All five patients with pericardial effusion and all four patients with right ventricular volume overload due to atrial septal defect were properly identified Four of the five patients with hypertrophic obstructive cardiomyopathy were recognized with one false negative occurring There were also one false negative and three proper diagnoses in the four patients with con gestive myopathy seen in this series One patient with congestive myopathy was excluded from this study because the heart was so large that the

Table I Accuracy of transducer array

Condition	*Patients*	*Correct diagnosis*	*False positive*	*False negative*
Mitral valve prolapse	15	15	1	0
Mitral stenosis	13	13	2	0
Pericardial effusion	5	5	0	0
Atrial septal defect	4	4	0	0
Hypertrophic myopathy	5	4	0	1
Congestive myopathy	4	3	1	1
Apical left ventricu lar aneurysm	1	1	0	0
Subtotal	47	45	4	2
Normal coronary artery disease left ventricular volume overload	33			
Total	80			

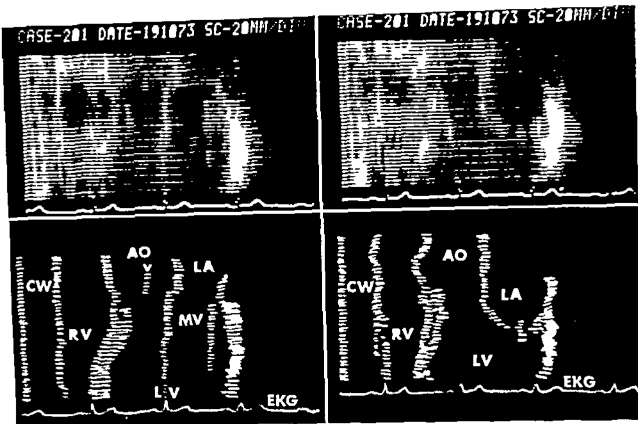


Fig 2 *Left top* Photograph of the oscilloscope image of a normal subject produced with the ultrasonic multiple transducer instrument Two frames are electronically interlaced to provide a 40 line picture The ECG is displayed at the bottom of the screen and moves from right to left i e end-diastole is indicated since the P wave has been inscribed but the QRS complex has not yet appeared *Left bottom* Diagram of the ultrasonic image above with cardiac structures labeled The open mitral valve leaflets *(MV)* are seen within the left ventricle *(LV)* and below the left atrium *(LA)* Also the closed aortic valve *(v)* is seen within the aortic root *(AO)* The interventricular septum is represented between the right ventricular cavity *(RV)* and the *LV* The chest wall *(CW)* echoes are shown to the left *Right top* Photograph of the same subject at end systole The aortic valve echoes are not seen and the closed mitral valve is well visualized. *Right bottom* Diagram of the ultrasonic image above Abbreviations are the same as in the left panel.

16 cm visualized depth was insufficient to include the posterior wall of the heart In one patient a left ventricular aneurysm near the cardiac apex was recognized The correct diag nosis was made in 45 of the 47 patients in whom the diagnosis was possible from the multiple transducer system

By reviewing the records of the laboratory during the time of this study it is estimated that 130 patients were available for inclusion in this series because of available hemodynamic and angiographic data for correlation Therefore ultrasonic studies of diagnostic quality were obtained in 62 per cent of the available patients Of the patients with records of diagnostic quality 41 per cent were in a group composed of several categories that could not be recognized as sepa rate categories on the basis of the qualitative criteria used here

Discussion

The construction of this multiple transducer imaging system by Bom and Hugenholtz provides an opportunity to have a high quality real time image of the interior structures of the intact beating heart It is difficult to appreciate the type and amount of information available from such a presentation unless the system is seen in real time by viewing the oscilloscope the video tape or the film record Single frames from such records as presented in Figs 2 and 3 are not truly represent ative of the quality of the image since the motion of the image is the main factor allowing recogni tion of the cardiac structures and their normal and abnormal motion When using the system it was immediately apparent that new criteria for diagnosis of such ultrasonic records would be needed It was possible to look at the pattern on one transducer line and try to use conventional

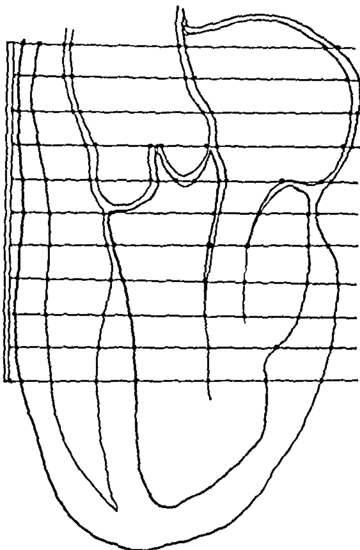


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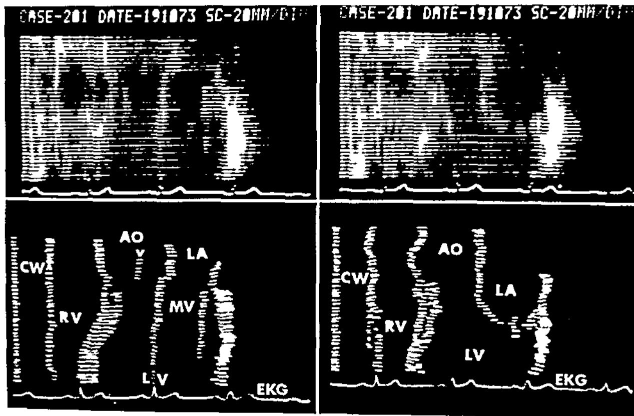


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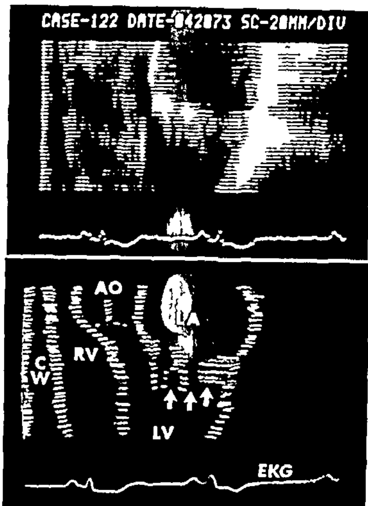


Fig 3 *Top* Photograph of the oscilloscope image of a patient with mitral stenosis produced with the ultrasonic multiple transducer instrument at end diastole Two frames are electronically interlaced to provide a 40 line picture *Bottom* Diagram of the ultrasonic image above with cardiac structures labeled as in Fig 2 Arrows indicate the multiple echoes from the open mitral leaflets Note the closed aortic valve echoes in the center of the aortic root *(AO)* There is a very large left atrium relative to the aorta and left ventricle (compare with Fig 2)

echocardiographic criteria for diagnoses However, the ability to visualize much of the heart in an "angiographic format provided additional information The first 22 patients studied with this system were not included in the present series since this was the time needed to put the system in order electronically and to become familiar with the system with regard to placement of the transducer proper amplification of the signal, recording of the image and preliminary criteria for diagnoses

All of the 15 patients with the mitral valve prolapse syndrome showed relatively small hearts The left atrium of these patients was either qualitatively normal in size or moderately enlarged compared to the right ventricle and aorta The distinctive feature in these patients included a very high amplitude motion of the anterior mitral leaflet During systole the anterior and posterior leaflets were seated higher in the left atrium than was seen in the normal patients and in patients without the prolapsing leaflet syndrome Because of this posterior placement during systole, the leaflet underwent a very great excursion at the onset of diastole and full mitral valve opening This opening was accomplished with an undulating motion of the anterior leaflet The portion of the anterior leaflet nearest the annulus apparently moved an instant before the mid and lower portion of the leaflet and this mid and lower portion moved with a whipping motion with diastolic opening The typical early diastolic opening and late reopening with atrial systole was seen in all of these patients In addition a large number of echoes from the anterior leaflet were seen and this made the leaflet look quite thick, although close inspection of each transducer line showed this appearance to be due to many discrete echoes from the anterior mitral leaflet in these cases

The 13 patients with mitral stenosis showed relative immobility of the mitral valve leaflets and multiple echoes from the area of the leaflets In addition, a large left atrium relative to the aorta and left ventricle was seen in each patient (Fig 3) A third criteria for the diagnosis of mitral stenosis was the rather slow and even filling rate during diastole In two patients mitral stenosis was erroneously diagnosed because of an apparently large left atrium with slow left ventricular filling These were patients with cardiomyopathy in whom both of these findings were confirmed by single transducer echocardiography but they were not due to intrinsic mitral valve disease

Pericardial effusion was recognized as an echo free space posterior to the posterior left ventricular wall and in some cases an echo free space anterior to the anterior right ventricular wall The apical one third of the anterior heart wall was separated from the chest wall in all five cases with posterior effusion In three of the five cases the whole heart could be seen to oscillate within the pericardial cavity with each heart beat

The four patients with atrial septal defect showed enlargement of the right ventricle relative to the left ventricle and an abnormality of motion of the interventricular septum In the patients without right ventricular diastolic

volume overload the systolic motion of the apical area of the interventricular septum was away from the transducer while the membranous septum nearest junction with the aorta moved toward the transducer The pivot point of the septum was in the upper third of this structure in patients without right ventricular volume over load In the patients with this condition the pivot point of the septum was very near the apex so that virtually all of the interventricular septum was moving toward the transducer during systole Apparently this was due to a large volume of blood going through the right ventricle with the anterior right ventricular wall and apex of the heart being attached to the chest wall and the left ventricle moving towards the chest wall with each systolic ejection

Without quantitative criteria the proper diag nosis was missed in one patient with hyper trophic myopathy and in one patient with congestive myopathy The possibility of hyper trophic obstructive myopathy was raised in the presence of a relatively normal sized ventricular chamber with disproportionately thick walls and/or asymmetrical septal thickening with respect to the left ventricular posterior wall The abnormal systolic motion of the anterior mitral leaflet seen with conventional echocardiography was quite difficult to appreciate due to its pres ence in a relatively small and localized area of the anterior leaflet The most mobile portion of the leaflet near its attachment to the chordae tendi neae did show this in patients with obstruction but its presence had to be searched for after suspicion of the condition due to the thickened walls and relatively small chamber Patients with a very large heart and low ejection fraction by these qualitative criteria were suspected of having congestive myopathy This was true in three of the four cases with this condition however one patient was erroneously placed in this category and one patient in this category was missed

Since the transducer is of sufficient length to show the whole heart from aorta to apex only in relatively small hearts it was necessary to move the transducer during the examination in order to visualize the whole heart in most adult patients It was difficult to visualize the cardiac apex with clarity in the majority of patients This is prob ably the result of motion of the cardiac apex in a plane perpendicular to the path of the sound beams However it was possible to recognize a moderate sized apical area of left ventricular dyskinesis in one patient In one patient with the mitral valve prolapse syndrome and bacterial endocarditis a mass of echoes was seen to move in continuity with the posterior leaflet of the mitral valve and was thought to represent a mass of vegetations on this leaflet This was confirmed by a similar pattern on the conventional echocardio gram while no abnormality of the posterior mitral valve leaflet could be seen on the angiogram

After this series of patients was collected one patient with a left atrial mass diagnosed at another institution was examined An ellipsoid mass of echoes was seen to move from the left atrium to the left ventricle during diastole and to move back through the mitral valve into the left atrium during systole It was thought that this condition would have been recognized using the multiple transducer system even if it had not been suggested on the basis of previous informa tion

With this new instrument one may use one or a combination of three types of criteria for the diagnosis of heart disease A normal or abnormal pattern of a specific structure such as the mitral valve may be appreciated One may assess the relative and possibly the absolute size of the cardiac chambers individually and in contrast with other cardiac structures And one may judge the dynamic patterns of filling and emptying of the cardiac chambers during the cardiac cycle With reference to conventional echocardiogra phy the new transducer system is less accurate in most conditions This is due to two considera tions apparently First very little experience has been gained with the new system and the criteria such as those set out in this paper must be supplemented further Second the prototype equipment used in this study did not provide the ability to write out the signals from an individual transducer in a time motion mode for measure ment and added recognition This ability has been developed recently and it is thought that the diagnostic accuracy of this equipment will be improved with this modification The great advantage of the multiple transducer system is the presentation of an image of the heart in two dimensions that is recognizable to any physician acquainted with cardiac anatomy and angiogra phy The ability to visualize most of the heart in two dimensions and then pick a single transducer

that is intersecting an area of the interest within the heart for presentation of a time motion recording should not only improve the accuracy of the technique but considerably simplify the procedure of echocardiography

An extension of the use of this technique with the development of methods of quantitating the ultrasonic image has been reported [1] We believe that this type of apparatus shows great promise for diagnosis and study of patients with heart disease The ability to record cardiac motion in this way presents an excellent opportunity both to study the volume changes of the heart without influencing the measured parameters and to make an unlimited number of serial observations The equipment used in this study is an early model and it is expected that considerable improvement of this model and other such systems will be forthcoming However it is appropriate to say that a very good quality image is presently available and offers a simplified and relatively accurate means of assessing heart disease At this point conventional echocardiography and cardiac imaging using the multiple transducer array system are supplementary rather than competitive techniques Anatomic location of structures and reassurance that the conventional echocardiogram gives representative data from the cardiac structures are available using the multiple transducer array system This report has outlined the types of cardiac disease which may be and those which may not be easily evaluated with this form of ultrasonic study

Summary

Eighty patients with various forms of heart disease were studied with the use of a newly developed ultrasonic system having 20 transducers arranged in a linear array This system allows visualization of the heart in two dimensions in real time All 15 patients with the mitral valve prolapse syndrome 13 patients with mitral stenosis, five patients with pericardial effusion four patients with atrial septal defect and one patient with left ventricular dyssynergy were properly recognized with this system One of five patients with hypertrophic myopathy and one of four patients with congestive myopathy were not recognized with this system Criteria for the recognition of these conditions are presented as well as the probable cause for false positive and false negative diagnoses in this series Since only qualitative criteria were used, it was not possible to differentiate patients with coronary artery disease or patients with left ventricular volume overload from patients without cardiac pathology The accuracy of this new system was judged against the clinical examination, conventional echocardiography, cardiac catheterization, and left ventricular angiography It is assumed that the criteria for diagnosis developed during this study will be supplemented and the equipment improved in the future however, the ease of operation of this system and the relative accuracy of diagnosis at this stage of its development are extremely interesting It presents an excellent opportunity to obtain additional information about the cardiac patient without using invasive procedures and without risk

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The effect of congestive heart failure on quinidine pharmacokinetics

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Quinidine is an important antiarrhythmic agent whose therapeutic effects and toxicity have been related to its serum concentration Very little information is presently available[2] concerning the pharmacokinetics of quinidine and factors important in regulating its dosage have not been determined Attempts have recently been made to calculate quinidine dosage regimens[3] but these calculations have been based on pharmacokinetics in healthy patients Recent reports [5] indicate that quinidine and other drugs may perform differently with respect to absorption distribution metabolism and elimination in diseased patients but very little quantitative information on these pharmacokinetic parameters is presently available

Congestive heart failure is known to induce a decrease in perfusion of vital organs such as liver kidney and gut as a result of a decrease in cardiac output It is reasonable to speculate that persons with this disease could eliminate drugs more slowly due to decreased perfusion of the kidney and could absorb drugs more slowly due to decreased perfusion of the intestinal tract Although little attention has been directed to the question of the effects of regional blood perfusion on drug pharmacokinetics intact organ systems utilize blood circulation as an integral part of their function and therefore blood flow must be considered as a potential rate limiting step Other workers[7] have implicated cardiac arrhythmias myocardial infarction and profound states of shock as causative agents in decreased peripheral perfusion Recent review articles [9] have stressed

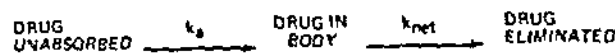


Fig 1 One compartment open model.

the increasing clinical awareness of changes in splanchnic and regional blood perfusion under pathologic conditions but the possibility of changes in human pharmacokinetics resulting from these conditions has not been thoroughly investigated Studies in our laboratories[11] [1] have shown that decreased blood perfusion of the intestine can lead to a dramatic reduction in drug absorption rate This report relates the therapeutic effects and toxicity of quinidine in congestive heart failure patients to changes in the absorption and distribution pharmacokinetics of these patients

Experimental methods

In the study of Bellet and colleagues[5] serum quinidine concentrations were determined at 2 4 6 and 24 hours following oral administration of 600 mg of quinidine sulfate in ten normal subjects and in ten patients with congestive heart failure Cumulative urinary excretion of quinidine was also determined at 24 hours In the study of Ditlefsen [3] blood quinidine concentrations were determined at 2 4 6 8 and 12 hours following the intramuscular injection of 840 mg quinidine chloride in ten normal subjects and in nine congestive heart failure patients Cumulative urinary quinidine excretion was also determined at 12 and 24 hours The quinidine blood and urinary data from the studies of Bellet and co workers and Ditlefsen[3] was fitted to a one compartment open pharmacokinetic model (see Fig 1) using the SAAM25 nonlinear regression program of Berman and Weiss[1] in conjunction with an IBM 360-75 digital computer The rate constants for absorption (K) the rate constants

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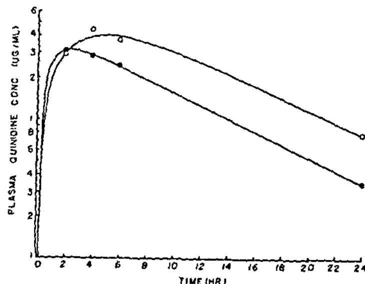


Fig 2 Plasma quinidine concentrations in normal subjects (●) and in congestive heart failure patients (o) following oral administration of 600 mg quinidine sulfate. The data points are the mean levels in ten subjects and the solid line represents the estimated concentrations based on the rate constants in Table I. Data from Bellet et al

for elimination (k_{el}) and the apparent volumes of distribution (V_d) were determined as indicated for each set of data. The total urinary excretion of quinidine was estimated in the study by Bellet and associates by using the trapezoidal rule with correction for the area in the tail of the curve.[15]

Results

A pharmacokinetic evaluation of the blood and urine data of Bellet and colleagues[3] shown in Table I and in Fig 2, indicates that congestive heart failure patients differ considerably from normal subjects. Congestive heart failure patients appear to absorb only about one half as much quinidine as normal subjects, absorb it more slowly, and have a smaller volume of distribution. This latter effect, which results in higher blood levels of quinidine, is most likely due to decreased perfusion of body tissues. This has been pointed out for lidocaine in similar type patients by Thomson and co workers.[1] As a consequence of the slower intestinal absorption rate, congestive heart failure patients reach peak quinidine concentrations at about four hours as compared to two hours in controls. Although renal perfusion may be decreased in congestive heart failure, quinidine elimination seems to remain unchanged in these patients. The computer estimated rate constants for elimination in Table I are nearly equal and the quinidine elimination down curves in Fig 2 fall in parallel when plotted on semilog

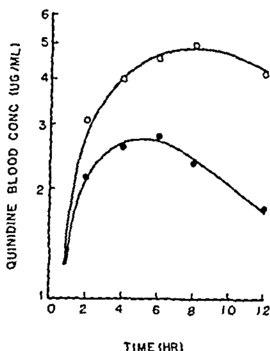


Fig 3 Quinidine blood concentrations in normal subjects (●) and in congestive heart failure patients (o) following the intramuscular administration of 840 mg of quinidine chloride. The data points are the mean levels in 9 to 10 subjects and the solid line represents the estimated concentrations based on the rate constants in Table II. Data from Ditlefsen

arithmic paper. This is in agreement with the recent report by Kessler and associates[4] which indicated no change in the elimination rate of quinidine in congestive heart failure patients. Renal and hepatic hemodynamics in reduced flow states are complex,[1] and this may account for the relatively unchanged elimination rate in congestive heart failure. The half life of 6.5 hours in normal subjects found here is in close agreement with the half life of 7.0 hours reported by Kessler and co workers.[4]

A pharmacokinetic evaluation of the blood and urine data of Ditlefsen[1] is reported in Table II and Figure 3. Peak quinidine concentrations again occur about two hours later in congestive heart failure patients than in normal subjects and are considerably higher. In congestive heart failure patients a decrease in the volume of distribution similar to that observed after oral administration of quinidine is indicated. In addition, the rate of absorption from the intramuscular site is much slower in the congestive heart failure patient than in the normal subject. This would suggest that for drugs whose action is required quickly, patients with congestive heart failure are poor candidates for the intramuscular route of administration. Although there are not enough

Table I Quinidine pharmacokinetic parameters following oral administration

Subjects	Absorption rate constant K	Absorption half life	Elimination rate constant K	Elimination half life	Apparent volume of distribution	Amount of quinidine excreted in urine	
						0-24 hr	0 ∞
Normal	1 00 hr	0 690 hr	0 107 hr	6.5 hr	33 3 L	129.3 mg	137 0 mg
Congestive heart failure	0 35? hr	1.97 hr	0 103 hr	6 7 hr	9 6 L	56 6 mg	64.3 mg

Estimated by trapez idal rule with tail c rrectio

Table II Quinidine pharmacokinetic parameters following intramuscular administration

Subjects	Absorption rate constant K	Absorption half life	Elimination rate constant K	Elimination half life	Apparent volume of distribution	Amount of quinidine excreted in urine	
						0-12 hr	0-24 hr
Normal	0 354 hr	1 96 hr	0 105 hr	6 6 hr	39 0 L	104.9 mg	155 6 mg
Congestive heart failure	0 1 7 hr	4 43 hr	0 105 hr	6 6 hr	16.3 L	75 " mg	136 5 mg

data points on the down curves to visually compare the elimination rates in this study the data fit well with similar elimination rate constants

Discussion

Patients with congestive heart failure have higher serum concentrations of quinidine than normal subjects receiving the same dose Al though changes in renal elimination have been suggested as the reason for this increase the present study suggests that a decrease in volume of distribution in congestive heart failure patients is the most likely cause of higher serum concen trations The decrease in distribution volume of quinidine is most likely due to decreased perfu sion of body tissues and thus congestive heart failure patients will have a greater fraction of the dose present in the vascular system Under these circumstances the heart and brain still well per fused could receive excessively high total amounts of quinidine resulting in possible cardiac and central nervous system toxicity This has been suggested as a possible cause of lidocaine toxicity in congestive heart failure patients

Quinidine appears to be more completely ab sorbed by congestive heart failure patients following intramuscular administration than fol lowing oral administration as indicated by the urinary excretion data in Table I and II In severe congestive heart failure blood flow to the gut may be decreased to such an extent that ischemia and infarction of the intestine may occur No similar effects have been reported for skeletal muscle under similar circumstances and may explain the difference in the amount of quinidine absorbed from the two sites Absorption of quinidine from the intramuscular injection site is slow under all conditions when compared to oral administra tion As a result both the controls and the congestive heart failure patients peak later following intramuscular administration than oral administration This may be a function of the intramuscular site selected since Schwartz and co workers have recently reported that the deltoid region is superior to others for rapid intramuscular absorption

Numerous reports have appeared in the litera ture suggesting methods to determine optimum dosing regimens for drugs with a relatively narrow therapeutic range such as quinidine When these dosage regimens are based on phar macokinetics in healthy individuals the calcu lated regimens may seriously overestimate the dose required since congestive heart failure patients maintain considerably higher blood levels of drugs than normal patients with similar doses Quinidine blood levels were found to be 41

per cent and 78 per cent higher in congestive heart failure patients than in normal subjects with similar doses following oral and intramuscular administration, respectively (see Figs 2 and 3) It has also been suggested for drugs which are eliminated by the kidney that urinary excretion data may be useful in regulating drug therapy In disease states such as congestive heart failure where absorption (and hence excretion) may be decreased but blood levels are increased, urinary excretion determinations may indicate that absorption is incomplete and the dose should be increased while in actual fact the opposite therapy may be indicated Caution should also be exercised when monitoring blood levels of drugs in congestive heart failure patients since a shift occurs in the time of maximum plasma concentrations Peak quinidine concentrations occur several hours later in congestive heart failure patients than in normal patients due primarily to the decrease in absorption rate For this reason serum quinidine determinations made at the time of peak concentration in normal patients will still be on the upcurve in congestive heart failure patients and may seriously underestimate the actual maximum concentrations occurring in these patients In Fig 2 quinidine levels peak at two hours in normal subjects and at four hours in congestive heart failure patients Quinidine concentrations determined in congestive heart failure patients at two hours would appear normal at 2 94 μg/ml as compared to 3 1 μg/ml in normal subjects After four hours, however the quinidine concentration in congestive heart failure patients would have increased 50 per cent to 4 38 μg/ml while the concentration in normal patients would have decreased Thus the time at which blood samples are taken is very important in regulating drug therapy in patients with congestive heart failure

Summary

Quinidine is an effective antiarrhythmic agent whose therapeutic effects and toxicity have been related to its serum concentrations Many patients with cardiac arrhythmias also suffer from congestive heart failure It is well documented that congestive heart failure can reduce blood perfusion to many regions of the body and could conceivably alter drug pharmacokinetics A pharmacokinetic evaluation of two sets of quinidine data in congestive heart failure patients indicates that congestive heart failure reduced the rate of absorption and volume of distribution following oral or intramuscular administration of quinidine Furthermore, the amount of quinidine absorbed following oral administration is reduced, but congestive heart failure does not appear to alter the elimination rate of quinidine The interpretation of the data presented herein strongly suggests that the site of administration, extent of distribution and rate of absorption must be considered when determining dosage regimens in congestive heart failure patients since normal dosages in these patients result in abnormally high serum quinidine concentrations

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Comparative systemic and regional hemodynamic effects of dopamine and dobutamine

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Dopamine has recently been released for treatment of shock and congestive heart failure Dobutamine is currently under investigation for the same conditions Both sympathomimetic amines exert positive inotropic actions but cause different effects on the peripheral vasculature Dopamine produces vasodilation of renal[1, 3] and mesenteric[4] vascular beds by action on a putative dopamine receptor As the dose of dopamine is increased, vasoconstriction occurs and a pressor response ensues[5] Dobutamine is a relatively cardiospecific beta adrenergic agent and produces little effect on mean blood pressure in man[9, 10] and dog[11, 12] When the drug is injected in the femoral artery of the anesthetized dog however beta adrenergic vasodilation and less prominant alpha adrenergic constriction occurs Within the same dose range renal vasodilation could not be demonstrated[11] Most previous studies assessing the cardiovascular responses of dopamine or dobutamine have used intravenous or intraarterial injections In the present study we compared the regional and systemic hemodynamic effects of intravenous infusions of these drugs in the anesthetized dog

Methods

Eight mongrel dogs, weighing 18 to 22 kilograms, were anesthetized with 30 mg per kilogram of pentobarbital sodium and intubated with a tracheal cannula A polyethylene catheter was placed in a brachiocephalic vein for infusion of drugs bilaterial cervical vagotomy was performed Catheters were placed in the thoracic aorta and left ventricle for pressure measurements The maximum rate of rise of left ventricular pressure (dP/dt) was obtained with an active operational amplifier circuit

Cardiac output was determined by the right heart thermal washout technique[13] A Swan Ganz thermistor tipped catheter was advanced into the pulmonary artery via a femoral vein and the saline indicator was injected at the level of the right atrium through a catheter advanced down the left external jugular vein The integral of the temperature time curve was obtained with a Thermodilution Cardiac Output Meter (Model 72 9, Columbus Instruments) The cardiac output values used in this study were the means of two to five determinations per observation period

Through a flank incision, the left renal and superior mesenteric arteries were exposed and dissected free of adjacent tissue The blood flow through each artery was determined with electromagnetic flowprobes Femoral blood flow was measured by an electromagnetic flowprobe placed around the femoral artery on the side contralateral to the cannulated femoral vein Zero reference flow for each artery was determined by occlusion of the vessel distal to the flowprobe The mesenteric renal and femoral vascular resistances were calculated by dividing the mean aortic pressure (in millimeters of mercury) by the respective blood flows (in milliliters per minute) The percentage of cardiac output perfusing the mesenteric ($\%CO_M$) renal ($\%CO_R$), and femoral ($\%CO_F$) vascular beds was calculated by dividing the respective blood flows by the cardiac output and multiplying the quotient by 100 Heart rate

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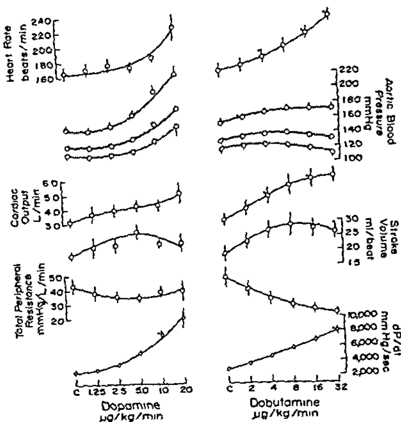


Fig 1 Systemic hemodynamic effects of dopamine and dobutamine Values are mean ± 1 standard error of mean
Significantly different from control ($p < 0.05$)
Significantly different from control ($p < 0.01$)

was recorded with a cardiotachometer All measured parameters were continuously recorded on a Beckman Type RM Dynograph

Solutions of dopamine and dobutamine were prepared daily and infused with a Harvard infusion pump the order of drug infusion was altered Dopamine was infused sequentially at rates of 1 25 2 5 5 10 and 20 µg per kilogram per minute and dobutamine was infused at rates of 2 4 8 16 and 32 µg per kilogram per minute All doses were calculated as the weight of base Each infusion rate was maintained for 15 to 20 minutes to allow for stabilization of all measured variables at which time cardiac output determinations were made and data measurements taken After terminating the infusion of one drug 30 to 60 minutes were allowed to elapse before a second set of control measurements were taken and the second drug infusion begun

The mean and standard error of the variables at each drug infusion rate were calculated and statistically significant changes from control were determined with a paired t test

Results

Systemic hemodynamic effects The cardiac and systemic hemodynamic effects of dopamine and dobutamine are illustrated in Fig 1 Bigeminy occurred in three of the eight dogs at the 20 µg per kilogram per minute dopamine infusion rate when the mean aortic pressure exceeded 185 mm Hg Therefore only five animals are represented at this dose level The heart rate became significantly elevated at the 10 and 20 µg per kilogram per minute infusion rates of dopamine In contrast dobutamine produced a dose related chronotropic effect increasing heart rate an average of 70 beats per minute at the highest infusion rate of the drug

Both amines produced a progressive widening of pulse pressure At the 10 µg per kilogram per minute infusion rate of dopamine the mean as

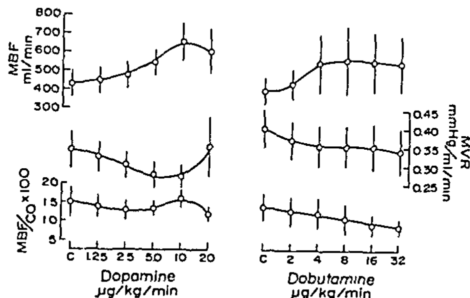


Fig 2 Mesenteric hemodynamic responses to intravenous infusions of dopamine and dobutamine Superior mesenteric artery blood flow (*MBF*) determined by electromagnetic flowprobe *MVR* superior mesenteric artery vascular resistance *MBF/CO × 100* per cent of cardiac output perfusing mesenteric artery Values are mean ± 1 standard error of mean

Significantly different from control ($p < 0.05$)

**Significantly different from control ($p < 0.01$)

well as the systolic and diastolic pressures began to increase Dobutamine on the other hand, produced only a slight increase in systolic pressure but the mean pressure was not changed

Dopamine increased cardiac output from 3 24 ± 0 34 to 5 01 ± 0 68 L per minute at the 20 μg per kilogram per minute infusion rate Total peripheral resistance was decreased by 2 5 and 5 0 μg per kilogram per minute of dopamine but returned to control at the 20 μg per kilogram per minute infusion rate Dobutamine produced prominent increases in cardiac output from 3 14 ± 0 42 to 6 05 ± 0 47 L per minute at the 32 μg per kilogram per minute rate The peripheral resistance decreased progressively in response to dobutamine since mean aortic pressure was not significantly affected Both dopamine and dobutamine produced dose related increases in dP/dt and the dopamine dose response curve was steeper than that for dobutamine, most likely due to the increased afterload

Mesenteric hemodynamic effects (Fig 2) Dopamine infusions progressively increased mesenteric blood flow from 430 ± 68 to 662 ± 106 ml per minute at the 10 μg per kilogram per minute infusion rate This increased flow was accompanied by decreased mesenteric resistance indicating active vasodilation Increasing the dopamine infusion rate to 20 μg per kilogram per minute decreased mesenteric blood flow by approximately 55 ml per minute and increased mesenteric vascular resistance to the control level The $\%CO_M$ was essentially unchanged

The average mesenteric blood flow increased in response to dobutamine infusions but the changes were not statistically significant Two of the animals exhibited no change in mesenteric blood flow and the flow in one animal actually decreased Additionally, at the 16 and 32 μg per kilogram per minute infusion rates the mesenteric blood flow in six of the eight dogs decreased from the flow observed at the previous dose level The mesenteric vascular resistance was decreased at the 32 μg per kilogram per minute dobutamine infusion rate The $\%CO_M$ decreased from a control value of 13 8 ± 3 4 to 8 8 ± 2 2 per cent at the highest dobutamine infusion rate

Renal hemodynamic effects (Fig 3) Renal blood flow increased in response to each infusion of dopamine up to 10 μg per kilogram per minute but the increase above control was less at the 20 μg per kilogram per minute infusion rate There was a simultaneous decrease in renal vascular resistance in response to low doses of dopamine again indicative of an active vasodilation but the resistance returned to the control level at the 20 μg per kilogram per minute dopamine infusion rates The mean $\%CO_R$ was increased by dopamine infusions but was statistically significant only at the 10 μg per kilogram per minute

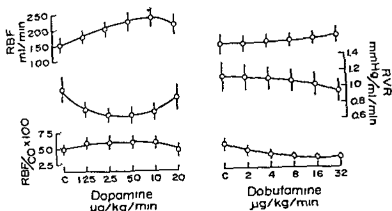


Fig 3 Renal hemodynamic responses to intravenous infusions of dopamine and dobutamine Renal blood flow (*RBF*) determined by electromagnetic flowprobe *RVR* renal vascular resistance *RBF/CO × 100* per cent of cardiac output perfusing renal artery Values are mean ± 1 standard error of mean
Significantly different from control ($p < 0.05$)
Significantly different from control ($p < 0.01$)

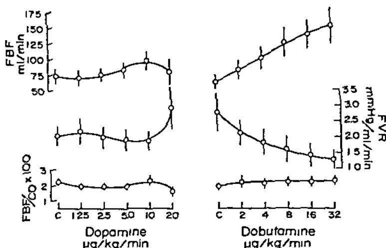


Fig 4 Femoral artery hemodynamic responses to intravenous infusions of dopamine and dobutamine Femoral blood flow (*FBF*) via electromagnetic flowprobe *FVR* femoral vascular resistance *FBF/CO × 100* per cent cardiac output perfusing femoral artery Values are mean ± 1 standard error of mean
Significantly different from control ($p < 0.05$)
Significantly different from control ($p < 0.01$)

infusion rate Dobutamine did not increase renal blood flow and renal vascular resistance decreased only at the 32 µg per kilogram per minute infusion rate The $\%CO_R$ was significantly decreased at all doses above 2 µg per kilogram per minute

Femoral hemodynamic effects (Fig 4) Only the 10 µg per kilogram per minute infusion rate of dopamine significantly increased femoral blood flow and femoral vascular resistance was increased at the 20 µg per kilogram per minute infusion rate The $\%CO_F$ was unchanged at all infusion rates of dopamine Dobutamine on the other hand produced dose related increases in femoral blood flow and decreases in femoral vascular resistance with a constant $\%CO_F$

Discussion

A large number of sympathomimetic amines are available which increase cardiac contractility These amines differ however in their peripheral vascular effects At one extreme isoproterenol

exerts almost equal beta adrenergic action on the heart and blood vessels but its use is often limited by tachycardia and a decrease in blood pressure[15] At the other extreme, norepinephrine exerts intense vasoconstrictor effects which may reduce flow to essential vascular beds In the present study we have demonstrated that dopamine and dobutamine exert intermediate—but differing—peripheral vascular effects in the anesthetized dog

When myocardial contractility was increased *to approximately 50 per cent above control* dobutamine produced a greater increase in cardiac output and decrease in total peripheral resistance than did dopamine Dobutamine also produced a greater chronotropic response than dopamine An increase in heart rate has been observed in patients with congestive heart failure at the infusion rates of 8 to 10 μg per kilogram per minute dobutamine In the conscious dog, however the heart rate did not increase until a dose of 40 μg per kilogram per minute was attained As in previous studies in animals and man the present study demonstrated a greater separation of the inotropic and chronotropic effects of dopamine

The peripheral vascular effects produced by these two drugs demonstrate their diverse effects on redistribution of cardiac output Dobutamine had no consistent effect on either mesenteric or renal blood flow thus the per cent cardiac output perfusing these two beds decreased Dopamine however increased the mesenteric and renal blood flow without affecting the distribution of cardiac output On the other hand, dobutamine produced a greater increase in femoral blood flow than dopamine In conscious, nonvagotomized dogs infusions of dobutamine produced a similar redistribution of cardiac output toward the femoral vascular bed[14]

Increased chronotropic and pressor responses became apparent when the dopamine infusion rate reached 10 μg per kilogram per minute As the dose was increased further peripheral vasoconstriction occurred opposing the dilating effect in the mesenteric and renal vascular bed Dobutamine did not cause vasoconstriction Tachycardia however appeared to be a dose limiting factor

The results of this study suggest that dopamine and dobutamine should be useful in treatment of patients with myocardial failure The choice of the agent would depend upon the peripheral vascular effect desired

Summary

Dopamine and dobutamine are sympathomimetic amines with divergent peripheral vascular actions The renal, mesenteric, and femoral vascular and total systemic hemodynamic effects of these amines were compared in pentobarbital anesthetized dogs Both agents increased myocardial contractility Infusion rates of dopamine greater than 5 μg per kilogram per minute increased mean aortic pressure Dobutamine increased the systolic pressure but did not alter mean aortic pressure Dobutamine increased cardiac output more than dopamine Dopamine infusions up to 10 μg per kilogram per minute increased renal and mesenteric blood flow and decreased vascular resistance Dobutamine had negligible effects on the renal or mesenteric blood flow but produced dose related increases in femoral blood flow Dopamine did not significantly alter femoral hemodynamics These results more clearly define the systemic and regional vascular hemodynamic effects of these agents

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Hemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure

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Congestive heart failure (CHF) refractory to vigorous conventional treatment with digitalis and diuretics is not uncommon in clinical practice Recently potent peripheral vasodilators such as nitroprusside and phentolamine have been found useful in improving left ventricular performance in patients with left ventricular failure due to acute myocardial infarction (MI)[1-5] and chronic CHF with or without mitral regurgitation[6] The long term use of these drugs in clinical practice is seriously limited by the need for both continuous infusion and invasive hemodynamic monitoring

Such limitations are avoided by the use of sublingual nitroglycerin, which has been shown to have beneficial hemodynamic effects in patients with acute MI complicated by left ventricular failure[7] The use of this agent, however, is limited by its duration of action

The purpose of this study was therefore to determine whether a sublingual long acting peripheral vasodilator could be employed to obtain the beneficial hemodynamic effects of nitroprusside phentolamine, and nitroglycerin without the limitations for clinical use encountered with these drugs Isosorbide dinitrate a 'long acting' nitrate which can be administered sublingually or orally, was selected As a number of patients in this study had ischemic heart disease as the underlying etiology of CHF the effects of the drug on myocardial metabolism were also studied in five patients by means of coronary sinus blood flow, oxygen, and lactate measurements

Methods

Patient population All patients were studied in the Myocardial Infarction Research Unit at Cedars Sinai Medical Center Following informed consent 12 patients 37 to 77 years of age, with chronic CHF diagnosed on the basis of dyspnea cardiomegaly, basilar râles elevated jugular venous pressure, and signs of pulmonary hypertension were studied (Table I) The etiology of heart failure included previous myocardial infarction (8), coronary artery disease (CAD) without infarction (1), primary cardiomyopathy (1) hypertensive cardiovascular disease (1), and rheumatic heart disease with prosthetic aortic and mitral valves (1) Six patients had associated mitral regurgitation All patients had been previously treated with standard digitalis, diuretic, and sodium restriction regimens Whenever possible previous medications were withheld for 24 hours prior to study

Hemodynamic and metabolic measurements All recordings were made with the patient in the supine position

Arterial pressure (AP) was monitored continuously through a 20 gauge cannula inserted into the radial artery Right atrial (RA), pulmonary

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Table 1 Clinical data

Patient	Age	Sex	Etiology CHF	Previous Rx	Comments
D C	65	M	CAD 3 MI ↓ BP	Digoxin furosemide	Mitral, tricuspid regurgitation
G K.	65	F	CAD 1 MI	Furosemide	
L. K.	77	F	CAD 1 MI	Digoxin furosemide	Mitral regurgitation
M. W	72	F	Recent MI	Digoxin furosemide	Mitral regurgitation, severe pulmonary congestion
H S	73	M	CAD 4 MI	Digoxin furosemide	Mitral regurgitation
B K.	37	F	Cardiomyopathy	Digoxin furosemide	Normal coronary angiography
J W	60	F	CAD no MI	Digoxin furosemide NTG Sorbitrate	Mitral regurgitation
M. P	6?	M	CAD 1 MI	Digoxin furosemide	Mitral, tricuspid regurgitation
M. T	77	F	↓BP	Digoxin	Severe pulmonary congestion
S C	51	F	CAD 1 MI	Digoxin furosemide	LBBB
M. L.	59	F	Rheumatic heart disease with aortic and mitral prostheses	Digoxin quinidine Coumadin	Tricuspid regurgitation
L C	67	M	CAD 1 MI	Digoxin furosemide	

BP = blood pressure

artery (PA) and pulmonary capillary wedge (PCW) pressures and cardiac output (CO) were recorded by use of a balloon tipped, flow directed triple lumen catheter Cardiac output was measured by the thermodilution technique[9,10] Venous capacitance (VC) was measured in eight patients with the equilibration method and a mercury in rubber strain gauge plethysmograph[1] The collecting pressure used was 30 mm Hg

Coronary sinus flow was measured in five cases with the constant infusion thermodilution technique[11] In these five cases simultaneous samples of systemic arterial pulmonary artery and coronary sinus blood were analyzed for pH pCO_2 and pO_2 by a pH gas analyzer Model 113 and hemoglobin saturation was determined with a co oximeter Model 182 Samples of blood were also taken for determination of lactate concentration by an automated modification of the enzymatic method of Hohorst

Derived hemodynamic and metabolic parameters were calculated as follows

Cardiac index (CI) = CO/body surface area (BSA) (ml/M^2)

Stroke volume index (SVI) = SV/body surface area (BSA) (ml/M^2)

Systemic vascular resistance (SVR) = $(\overline{AP} - \overline{RA})$ (mm Hg)/CO (L/min.) × 80 (dynes/sec /cm^5)

$\Delta P/\Delta t$ = (DAP − $\overline{PCW}$)/PEP (mm Hg/sec) where PEP = pre-ejection period (msec.) and is derived from total electromechanical systole (QS_2) − left ventricular ejection time (LVET) (msec.) simultaneously recorded from external carotid pulse tracing and electrocardiogram (ECG) DAP = arterial end-diastolic pressure (mm Hg)

Myocardial oxygen consumption (ml/min) = (arterial − CS O_2 content [ml/100 ml]) × CSF (ml/min) × 10

Myocardial lactate extraction (%) = $\frac{\text{Arterial} - \text{coronary sinus lactate (mg/100 ml.)}}{\text{Arterial}} \times 100$

Protocol Sublingual isosorbide dinitrate was administered as 5 mg (three patients) 10 mg (six patients) or 15 mg (three patients) based upon the magnitude of heart failure as assessed by mean pulmonary capillary wedge pressure ($\overline{PCW}$) and level of arterial pressure (AP) Complete dissolution and absorption of the tablet was assured by having the patient moisten his mouth before drug administration (Fig 1)

Control hemodynamic and metabolic data were recorded After 15 minutes hemodynamic measurements were repeated to insure stability of controls Following drug administration venous capacitance was measured at 5 minute intervals and hemodynamic parameters were recorded at 15 minute intervals Metabolic studies were performed during peak drug effect This was defined as that time at which greatest change was seen in cardiac output

Results

The hemodynamic and peripheral vascular effects of isosorbide dinitrate became evident within 15 minutes in all patients reached maximum levels at 15 to 45 minutes and persisted in reduced magnitude for 75 to 90 minutes

The maximum changes in hemodynamic parameters for each individual were defined as occur

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Arterial pressure (AP) was monitored continuously through a 20 gauge cannula inserted into the radial artery Right atrial (RA) pulmonary

Table II Hemodynamic changes during isosorbide dinitrate therapy

Patient	HR (beats/min)	$\overline{AI}$ (mm Hg)	$\overline{RA}$ (mm Hg)	$\overline{PA}$ (mm Hg)	$\overline{PCW}$ (mm Hg)	CI (L/min/M)	SVI (mL/min/M)	SVR (dynes/sec/cm)	PVR (dynes/sec/cm)	ΔP/ΔT (mm Hg/sec)	VC (cc/100 cc)
D C											
C†	84	87	12	52	37	1.40	16	2,915	444		2.4[illegible]
I	83	81	4	36	28	2.05	29	2,029	277		3.28
G K											
C	109	84	7	30	30	1.62	16	2,714	318		
I	103	74	4	28	20	2.18	22	2,088	157		
L K											
C	85	89	13	37	27	1.58	19	3,111	350		
I	83	79	7	31	20	1.99	25	2,468	220		
M W											
C	101	75	4	37	27	1.33	13	2,953	477		
I	104	69	1	28	23	1.44	14	2,093	256		
H S											
C	72	101	7	24	19	2.58	36	2,589	185	323	2.90
I	76	96	5	15	12	2.40	30	2,541	100	408	3.20
B K											
C	89	81	13	31	17	2.24	26	2,088	189	276	3.15
I	78	80	8	22	14	2.68	36	1,[illegible]08	96	224	4.18
J W											
C	74	82	6	43	30	2.19	31	1,901	349	190	0.92
I	74	72	6	34	22	2.15	30	1,902	321	276	1.9[illegible]
M P											
C	64	85	16	40	25	1.60	26	2,523	423	336	1.65
I	62	68	13	38	18	2.06	32	1,481	324	365	4.22
M T											
C	110	107	16	44	29	2.25	21	3,194	407	3[illegible]	1.47
I	121	97	13	45	28	3.49	28	1,884	230	480	2.33
S C											
C	112	80	10	44	39	2.73	24	1,386	99	168	4.37
I	102	80	5	30	30	3.04	30	1,333	71	211	5.74
M L											
C	6	73	14	37	32	2.41	39	1,314	131	131	2.80
I	63	70	8	32	26	2.66	42	1,258	161	161	7.00
L C											
C	90	76	5	36	29	2.06	23	1,986	225	225	
I	82	68	3	23	14	2.34	27	1,600	2[illegible]6	256	
Mean											
C	88 ± 5	85 ± 3	10 ± 1	39 ± 4	28 ± 2	1.99 ± 0.13	24 ± 2	2,428 ± 168	302 ± 37	2[illegible]3 ± 31	2.46 ± 0.16
I	85 ± 5	78 ± 2	6 ± 1	30 ± 4	21 ± 2	2.37 ± 0.15	29 ± 2	1,918 ± 99	192 ± 26	298 ± 39	3.99 ± 0.24
Change	−3	−7	−4	−9	−7	+0.38	+5	−510	−110	+46	+1.53
Per cent	−3	−8	−40	− 3	−25	+20	+21	−21	−36	+18	+62
p	NS	< 0.0[illegible]	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02

HR, heart rate; $\overline{AI}$, mean arterial pressure; $\overline{RA}$, mean right atrial pressure; $\overline{PA}$, mean pulmonary arterial pressure; $\overline{PCW}$, mean pulmonary capillary wedge pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; VC, venous capacitance.

†C, control; I, isosorbide dinitrate.

the systemic and pulmonary venous pressures. This venous pooling effect even in the absence of CHF has been described previously.[1]

Increased forward cardiac output, the other important objective of therapy of CHF, was also observed following isosorbide dinitrate therapy in 10 of the 12 patients. An increased stroke volume with decreased left ventricular filling pressure suggests an enhanced cardiac performance. The mechanism of increased cardiac output is likely to

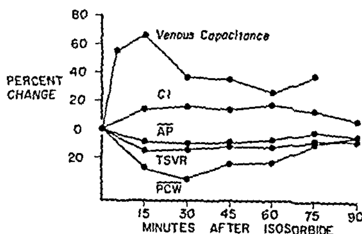


Fig 1 The effect of isosorbide dinitrate upon five hemodynamic parameters over the course of 90 minutes These data represent the mean per cent change from control values in 12 patients A substantial increase in venous capacitance is seen at 5 minutes with peak effect at 15 minutes All other hemodynamic parameters have peak effect at 15 to 30 minutes After 75 minutes these effects are markedly reduced Abbreviations $\overline{AP}$ mean arterial blood pressure *CI* cardiac index $\overline{PCW}$ mean pulmonary capillary wedge pressure *TSVR* total systemic vascular resistance

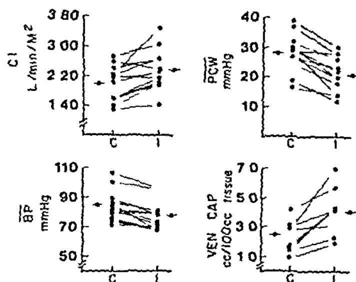


Fig 2 The hemodynamic response to isosorbide dinitrate in 12 individual patients Cardiac index increased in 10 patients remained unchanged in one and declined in one Pulmonary capillary wedge pressure decreased in all patients and arterial pressure decreased in 10 remaining unchanged in two Venous capacitance increased in all eight patients studied Abbreviations $\overline{BP}$ mean arterial blood pressure (mm Hg) *CI* cardiac index (L/min/M²) $\overline{PCW}$ mean pulmonary capillary wedge pressure (mm Hg) *Ven Cap* venous capacitance (c c/100 c c of tissue)

ring at the time of maximum cardiac output (Table II and Fig 2) These included a modest reduction in mean arterial pressure (−7 mm Hg) and substantial changes in right atrial (−4 mm Hg) and pulmonary capillary wedge pressure (−7 mm Hg) cardiac index (+0 38 L/min/M²) stroke volume index (+5 c c/min/M²) Notable reductions in systemic and pulmonary vascular resistances, −510 and −110 dynes/sec/cm⁻⁵, respectively, and an increase in venous capacitance (+1 53 c c/100 c c of tissue) also occurred Heart rate remained unchanged Changes in ΔP/Δt, an index related to left ventricular dp/dt, were studied in eight patients In seven patients, all with obstructive coronary artery disease ΔP/Δt increased during isosorbide dinitrate therapy The remaining patient, in whom ΔP/Δt decreased, had primary cardiomyopathy without coronary artery disease

In five patients myocardial metabolic studies were performed before and after drug administration (Table III) In all patients coronary sinus flow (−34 ml/min) and myocardial oxygen consumption (−3 6 ml/min) decreased during isosorbide dinitrate therapy No significant change occurred in arterial coronary sinus O_2 difference or transmyocardial lactate extraction

Discussion

The principal hemodynamic objectives of management of patients with chronic heart failure are to improve forward cardiac output and decrease pulmonary venous pressure Intravenous vasodilators such as phentolamine or nitroprusside fulfill these objectives and have been successfully applied in the management of patients with congestive heart failure The obvious disadvantages of such therapy are that they cannot be used for long term management and require closely supervised hemodynamic monitoring

This study demonstrates that sublingual isosorbide dinitrate, a vasodilator agent, may be used to improve left ventricular performance in patients with refractory and severe CHF and may be useful in long term management All patients exhibited significant reduction in pulmonary and systemic venous pressures and concomitant reduction in the symptoms and signs of right and left heart failure

The data in this study suggest that these changes were a result of changes in both systemic vascular resistance and venous capacitance Decreased resistance to ejection by the failing heart would be expected to increase ejection fraction and decrease left ventricular volume and filling pressure An increase in venous capacitance would allow venous pooling, thus reducing both

infarction This potential use is highlighted by well founded reluctance of many physicians to use digitalis in this setting and the recent emergence of potent vasodilators as effective therapy Our results suggest that study of the use of isosorbide in this clinical situation is warranted

Although this study demonstrates that isosorbide dinitrate may be effective in the management of refractory congestive heart failure some disadvantages should be remembered The duration of action does not usually exceed 90 minutes so that frequent drug administration may be a source of patient inconvenience Sudden unexpected hypotension and marked decrease in left ventricular filling pressure although infrequent may produce an adverse response For these reasons the arterial pressure left ventricular filling pressure and cardiac output should be monitored during the initiation of therapy If these facilities are not available the initial dose should not exceed 2 5 mg The chance of an adverse response is further minimized if the patient has clear cut evidence of increased left ventricular filling pressure If dizziness undue tachycardia or hypotension occur therapy should be discontinued

Summary

To assess the potential beneficial effects of a nonparenteral vasodilator sublingual isosorbide dinitrate (5 to 15 mg) was administered in 12 patients with chronic congestive heart failure refractory to conventional therapy Hemodynamic measurements were performed before and at 15 minute intervals after drug administration for 90 minutes Venous capacitance was measured at 5 minute intervals Myocardial metabolism was also studied in five patients before and after drug administration

Hemodynamic effects were characterized by a modest decrease in mean arterial pressure (85 ± 3 to 78 ± 2 [S E M] mm Hg) and substantial decrease in right atrial (10 ± 1 to 6 ± 1) pulmonary arterial (39 ± 4 to 30 ± 4) and pulmonary capillary wedge pressures (28 ± 2 to 21 ± 2) These changes were accompanied by an increase in venous capacitance (2 46 ± 0 16 to 3 99 ± 0 24 c c /100 c c of tissue) Along with a decrease in left ventricular filling pressure cardiac index increased (1 99 ± 0 13 to 2 37 ± 0 15 L/min /M²) No significant effect on heart rate was seen $\Delta P/\Delta t$ an index related to left ventricular dp/dt increased in all but one patient (253 ± 31 to 298 ± 39 mm Hg/sec) ($p < 0.02$ for all changes) in the face of decreased preload and afterload and unchanged heart rate suggesting improved contractile state A decrease in coronary blood flow (165 ± 13 to 131 ± 15 c c /min) and myocardial oxygen consumption (18 1 ± 1 6 to 14 5 ± 1 6 c c /min) was noted ($p < 0.02$) No change in arterial coronary sinus oxygen difference or lactate extraction was observed

These data demonstrate that the objectives of therapy in congestive heart failure namely improved forward output and decreased ventricular filling pressures can be achieved without metabolic deterioration by using sublingual isosorbide The mechanisms responsible are related to diminished impedance to ventricular ejection and peripheral pooling of blood Since the duration of action does not usually exceed 90 minutes frequent drug administration may be a source of patient inconvenience

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Table III Myocardial metabolism, five patients

	CSF* (cc/min)	A CS O_2 (vol %)	MVO (cc/min)	Lactate extraction (%)
Control	165 ± 13	11 4 ± 1 0	18 1 ± 1 6	36 ± 5 5
Isosorbide dinitrate	131 ± 15	11 2 ± 1 0	14 5 ± 1 6	40 ± 6 1
Per cent	–34	–0 2	–3 6	+4
P	< 0 02	NS	< 0 02	NS

CSF coronary sinus flow MVO myocardial oxygen consumption

Table IV Maintained improvement after 2 months of isosorbide treatment

	HR	$\overline{AP}$	$\overline{RA}$	$\overline{IA}$	$\overline{PCW}$	CI	SVI	SVR	PVR
5/73 C	79	103	8	41	23	1 8	23	2 610	307
5/73 I	80	99	6	37	18	2 0	25	2 286	193
7/73 I	68	80	3	21	9	2 3	34	1 717	124

For abbreviations see Table II

be a decrease in resistance to left ventricular ejection as previously described[16] In two patients the cardiac index did not increase In one patient (H S) who had sustained four previous myocardial infarctions with long standing heart failure PCW pressure decreased markedly early in the study suggesting that left ventricular filling pressure was reduced below that which was optimal[17] The other patient (J W) whose cardiac index did not increase (2 19 to 2 15 ml/min/M²), was the only patient treated previously with long acting nitrates (Sorbitrate for chronic angina) Isosorbide dinitrate caused limb flow to drop sharply and limb vascular resistance to increase (not shown in figures)

ΔP/Δt, an index closely related to left ventricular dp/dt increased during isosorbide dinitrate therapy, although both preload and afterload decreased and heart rate remained unchanged While not conclusive these unexpected findings are consistent with improved over all contractile state which might be contributory to improved cardiac performance The mechanism of any such improved over all contractility in the face of a known lack of direct inotropic effect of isosorbide dinitrate remains conjectural Reflex increase in inotropy is unlikely in the absence of an increase in heart rate Relief of myocardial ischemia and recruitment of previously hypofunctioning myocardial segments may result in an improved contractile state, as suggested by recent angiographic studies before and after nitroglycerin administration[18] Such improvement however, would not be expected in patients without coronary artery disease In this study the only patient who did not show an increase in ΔP/Δt was the one who had primary cardiomyopathy without obstructive coronary artery disease

The metabolic cost of enhanced mechanical performance, although investigated in only five patients, was consistent in all cases Since coronary blood flow decreased in these patients, reduced MVO_2 could be related to decreased coronary perfusion pressure In such an instance increased transmyocardial A V oxygen difference or a decrease in transmyocardial lactate extraction would be expected but neither was observed in this study The decrease in coronary blood flow and myocardial O_2 consumption, therefore are most likely related to decreased over all O_2 demand, which in turn reflects the observed decrease in preload and afterload despite some suggestion of increase in contractile state

Clinical application of isosorbide dinitrate therapy was begun in all of our patients following their hemodynamic study, and they were discharged from the hospital on chronic isosorbide therapy Nine patients have been treated with isosorbide dinitrate for 4 to 8 months and all of them are judged clinically to be improved Continued hemodynamic benefit has been documented in one 55 year old man studied after 2 months of such therapy (Table IV)

Although not investigated directly in this study, another important application of this mode of therapy may be in the treatment of left ventricular failure during acute myocardial

Complications of selective coronary arteriography by the Judkins technique and their prevention

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The techniques of Sones and Shirey and of Judkins are the two most commonly employed methods of selective coronary arteriography. Recently there have been several reports describing a higher incidence of morbidity and death with the use of the Judkins technique as compared to the Sones technique. However, Green and associates reported no death and two coronary artery occlusions in 445 selective coronary examinations performed by the Judkins technique in 1 year. Adams, Fraser, and Abrams also found that the incidence of death, myocardial infarction, and cerebral emboli with the Judkins technique was higher in institutions where less than 100 coronary examinations were performed per year as compared to those where more than 200 such examinations were performed annually. We have performed less than 100 transfemoral coronary examinations per year for the past 4 years at the New York Veterans Administration Hospital (average 92 studies annually). The incidence of complications in our experience has been no higher than that reported by other centers using the Sones technique or by centers performing more than 200 transfemoral examinations per year. The purpose of this report is to review the incidence and causes of these complications and to describe certain modifications in the use of the Judkins technique to minimize complications.

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Subjects and methods

Between July 23, 1970, and July 31, 1974, 377 selective coronary examinations were performed in 306 patients. The numbers of various procedures performed are shown in Table I. All patients were male except one. Their ages ranged from 22 years to 70 years. The clinical diagnoses of the 280 patients who underwent transfemoral selective coronary examinations are shown in Table II. The findings on coronary arteriography in these patients are summarized in Table III. About half of the procedures were performed by trainees with staff supervision.

Patients were fasted for 8 hours before the procedure and were not premedicated. All were inpatients. All underwent right and left heart catheterization, selective left ventriculography, aortography whenever indicated, and selective coronary arteriography. Renografin 76 was used for angiography in all patients. Coronary arteriograms were recorded by cinefluorography and on biplane serial cut films.

Left heart catheterization and left ventriculography were performed through a femoral artery (usually the left) separate from that to be used for coronary artery catheterization (usually the right). Prior to coronary artery catheterization a platinum tipped Cournand catheter is positioned in the superior vena cava. This catheter is used for emergency drug administration as well as for cardiac pacing in the event of persistent bradycardia not responding to intravenous atropine. A temporary standby pacemaker is inserted in all patients with advanced A-V block, bundle branch block, or bifascicular block. All patients with heart rate less than 100 beats per minute are given 0.4 to 0.6 mg. of atropine sulfate intrave

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Table IV Complications

	No of cases (351 total)	Complications % Total (3 13)	Treatment	Sequelae
Cardiac				
I Coronary artery dissection	0	–	–	–
II Acute myocardial infarction	1	0 28	Conservative	Uneventful recovery
III Ventricular fibrillation	4	1 13	D C countershock with return to normal sinus rhythm	Uneventful recovery (3) death (1)
Femoral				
I Subintimal dissection	0	–	–	–
II Thrombosis	3	0.85	Endarterectomy	Normal pulse
III Delayed bleeding	0	–	–	–
Peripheral emboli				
I Cerebral	1	0 28	–	Complete recovery
II Popliteal	2	0 56	Embolectomy	Normal pulse

changes produced by prior injection have returned to the preinjection state During episodes of symptomatic hypotension the catheter is removed from the coronary artery and blood pressure is raised with metaraminol infusion before any further injections are made The total duration from femoral artery puncture to end of coronary injections was from 30 to 40 minutes in most cases

Results

There were 11 complications and one death in 351 procedures performed by the Judkins technique (Table IV)

Ventricular fibrillation Four patients developed ventricular fibrillation (1 13 percent) All four were successfully defibrillated with return to normal sinus rhythm Three of the four patients were discharged without any ill effects due to the episode of ventricular fibrillation The fourth patient had developed complete A V block just before the onset of ventricular fibrillation He remained hypotensive despite right ventricular pacing and norepinephrine Emergency open heart surgery was performed with resection of a large anterior wall left ventricular scar mitral valve replacement and tricuspid annuloplasty He had low cardiac output and no blood pressure after he was taken off the cardiopulmonary bypass and finally died The mortality rate in association with coronary arteriography in this series was 0 28 percent

Acute myocardial infarction One patient developed acute inferior wall infarction following injection into the right coronary artery He had severe triple vessel disease and an uneventful postinfarction course

Femoral artery thrombosis Three patients developed femoral artery thrombosis (0 85 per cent) Two had severe peripheral vascular disease The third patient had severely reduced cardiac output and the same femoral artery was used for coronary arteriography and left ventriculography Successful thrombectomy was performed in all three patients

Popliteal embolus Two patients developed a popliteal embolus (0 56 per cent) Embolectomy was performed by the Fogarty catheter technique[10] with return of normal pulses

Cerebral embolus A probable cerebral embolus occurred in one patient (0 28 per cent) This patient had severe triple vessel disease and markedly reduced cardiac output There was sudden onset of left lower facial palsy and weakness of the right upper extremity at the end of the procedure He recovered completely in the next 24 hours It is not certain whether the cerebrovascular accident occurred due to hypotension during the procedure resulting in poor cerebral perfusion or due to small embolus

Discussion

Cardiac complications

Ventricular fibrillation The incidence of

Table I Number of selective coronary examinations

		No
I	Femoral	
	(a) Coronary arteries	294
	(b) Saphenous vein bypass graft	42
	(c) Internal mammary artery	15
II	Brachial	
	Coronary arteries	26
	Total	377

Table II Clinical diagnoses of 280 patients studied by the Judkins technique

	No
Coronary heart disease	202
Valvular heart disease	42
Cardiomyopathy	30
Others	6
Total	280

Table III Findings on coronary arteriography in 280 patients studied by the Judkins technique

		No
I	Three vessel disease (> 50% obstruction)	89
II	Two vessel disease (> 50% obstruction)	56
III	One vessel disease (> 50% obstruction)	55
IV	Others (< 50% obstruction in one or more vessels)	22
V	Normal	58
Total		280

nously about 5 minutes before coronary catheterization Sublingual or chewable isosorbide dinitrate (5 mg) is given just before coronary catheterization

The left coronary catheter is always advanced first A Teflon coated safety J guide wire is used to facilitate entry of this catheter The catheter is attached through a three way stopcock to a pressure drip of normal saline containing 5 U of heparin per milliliter The technique of Judkins[3] is precisely followed for all catheter manipulations The pressure at the catheter tip is continuously monitored No injection is made if the catheter tip pressure is unusually damped Free backflow of blood into the injection syringe must occur before any injection is made If there is any delay between injections (e g , when switching from cine to cut film recording) the catheter is flushed by a slow drip of heparinized normal saline Judkins recommended that if heparinized saline has to be infused through the coronary catheter, the latter should be withdrawn from the coronary artery We have regularly infused heparinized saline when the catheter is in the coronary artery and have not had any complications as a result of this

In the event of severe bradycardia at the end of an injection, frequent hard coughing by the patient promptly accelerates the heart rate in a majority of patients If this maneuver fails, the catheter is withdrawn from the coronary artery and intravenous atropine is administered If the bradycardia still persists cardiac pacing is instituted

When the injections in the left coronary artery are completed, the left coronary catheter is exchanged for the right coronary catheter over a guide wire Before the withdrawal of the left coronary catheter and before the insertion of the right coronary catheter the puncture wound is vigorously flushed with heparinized saline The right coronary catheter is advanced to just above the bifurcation of the aorta and the guide wire is removed Free backflow of blood should occur through this catheter before it is advanced any farther If there is no free flow of blood even after ensuring that the catheter tip is free in the aortic lumen, a clot is presumed to be present in the catheter tip In such instances, the catheter is removed while a slight suction is held with a syringe No pressure is applied over the vessel during the withdrawal of the catheter lest the clot at the catheter tip be detached and embolize peripherally The catheter is then checked for a clot and discarded This approach prevents carrying of the clot at the catheter tip to the central aorta where embolization to a vital organ can easily occur If the distal pulses are unchanged from before the study a second puncture is made in the femoral artery above the site of the previous puncture The need for second femoral artery puncture has been very infrequent in our experience Once good blood flow is established through the right coronary catheter it is advanced to the aortic root under continuous monitoring of pressure and manipulated into the right coronary artery

No injection is made into a coronary artery during an episode of chest pain or until ECG

of a left Judkins catheter in the aortic arch causing baroceptor stimulation We have not observed this phenomenon in any of our patients

Acute myocardial infarction The incidence of acute myocardial infarction in association with coronary arteriography is reported to be higher with the Judkins technique than with the Sones technique[4,5,7] In a majority of cases acute myocardial infraction occurs secondary to thromboemboli originating in the cardiac catheter or over the guide wire Prolonged spasm of a coronary artery[15] or prolonged wedging of the catheter against an obstructive atheromatous plaque may also cause myocardial infarction Acute dissection of a coronary artery leading to myocardial infarction has also been described Use of separate femoral arteries for left heart catheterization and for coronary arteriography reduces the number of catheters introduced through the same femoral artery for coronary catheterization to a maximum of two catheters The smaller the number of catheters introduced through the same artery the smaller is the chance of thromboembolic complications as long as the duration of catheter stay is not unusually prolonged

Another important aspect of the Judkins technique is that the left coronary catheter must always be used first In order to preserve the acute curve of this catheter it is essential to use a guide wire to advance the catheter to the proximal aortic arch If the left coronary catheter is the second or the third catheter to be advanced through the same femoral artery it can carry a clot at its tip and cause acute coronary embolism as it is advanced to the left coronary artery or when an injection is made This mechanism appears to be the cause of the high incidence of acute myocardial infarction in association with the Judkins technique reported by Takaro and associates In their description of the technique they mention that typically after left ventriculography or right coronary arterial injection or both the previously used catheter was removed after reintroducing the guide wire and exchanged for the left coronary catheter In their series 26 of the 33 patients with acute myocardial infarction showed evidence of left coronary artery involvement It is not advisable to use the left coronary catheter after any other catheter It appears that the high incidence of acute myocardial infarction reported by Takaro and associates[5] was largely due to left coronary occlusion and faulty technique and was preventable to a large extent Takaro Hultgren and Detre[7] have recently reported a significant reduction in morbidity and mortality rates with the Judkins technique in the Veterans Administration Cooperative Study of complications of coronary arteriography Although they attribute this improvement to systemic heparinization the improvement may have been in part the result of increased experience and skill of the angiographer

Peripheral vascular complications The incidence of local complications in the form of bleeding thrombosis pseudoaneurysm or subintimal dissection is reported to be 0 6 to 1 3 percent of cases studied by percutaneous transfemoral catheterization technique [1] Prospective studies of local complications of retrograde catheterization via brachial arteriotomy at Mayo Clinic[2] and Peter Bent Brigham Hospital[11] have shown a 12 2 and 28 per cent incidence of reduced or absent radial pulse respectively The incidence of local arterial complications is significantly lower with the Judkins technique as compared to the Sones technique (Table V) Two of the three patients with femoral artery thrombosis in our series had severe peripheral vascular disease We now use the Sones technique electively in patients with clear cut clinical evidence of severe vascular disease of the lower extremities

The incidence of popliteal emboli in our series was 0 56 per cent Prior to July 23 1970 we had used the same femoral artery for the passage of left ventriculography catheter (Teflon Gensini) and the left and right coronary catheter in 14 patients Three of the 14 patients (21 4 per cent) had popliteal emboli The use of separate femoral arteries for left ventriculography and for coronary arteriography has significantly reduced the incidence of peripheral embolization

Nejad and associates suggested systemic heparinization during catheterization to reduce the incidence of thromboembolic complications Walker and associates [1] and Eyer[2] have recently reported a striking reduction in thromboembolic complications by systemic heparinization during arteriography by the Judkins technique Some of their patients required protamine to obtain hemostasis at the arterial puncture site Judkins and Gander now use and recommend single dose total body heparinization as an effective method of further reducing thromboembolic complica

Table V Complications of selective coronary arteriography in various reported series

Ref	No of cases	Local thrombosis (%)	Peripheral emboli (%)	Acute myocardial infarction (%)	Ventricular fibrillation (%)	Death (%)
3	23-S	8 7	0	0	0	0
	52-J	3 8	0	1 3	12 0	0
11†	3 312-S	0 5	–	0 3	0 7	0 1
	642-S	2 3	–	0 9	1 7	–
4	413-S	9 5	–	0 5	2 2	0
	478-J	4 8	–	1 9	4 0	2 0
5	500-S	–	–	0 2	–	0 6
	1 800-J	–	–	1 8	–	2 4
9	445-J	1 0	0 45	0 45	0 22	0 45
7	21 124-S‡	1 67	0 03	0 22	1 15	0 13
	1 835-S§	1 3	–	0 43	1 79	0 32
	22 780-J‡	1 19	0 43	1 01	1 41	0 78
	1 910-J§	1 08	–	1 28	0 97	0 77
Present study	351-J	0 85	0 56	0 28	1 13	0.28

S Sones technique J Judkins technique
†This review consisted of the experience in 10 laboratories including Cleveland Clinic The over all number of procedures was 3 312 If the procedures done at Cleveland Clinic are excluded 642 procedures were done in the other nine laboratories
‡Results in overall survey
§Results in institutions performing fewer than 100 examinations per year

ventricular fibrillation has varied from 0 to 12 per cent in various series[3, 4, 7, 9, 11] The occurrence of ventricular fibrillation is reported to be more frequent with the Judkins technique than with the Sones technique (Table V) Slow clearance of contrast agent, high sodium content in the contrast agent, presence of acid base and electro lyte imbalance acute myocardial infarction and prolonged severe bradycardia are some of the causes that increase the risk of ventricular fibril lation, however, the cause may remain obscure in a number of cases Thirty of the 280 patients (transfemoral examinations) had performed exer cise 45 minutes prior to coronary arteriography for evaluation of their myocardial function Two of the four patients who developed ventricular fibrillation had performed exercise prior to coronary arteriography Although there is an increase in circulating catecholamines during exercise, the catecholamine level in the blood returns to control state within 10 minutes after exercise is terminated[12] Thus in these two patients exercise should not have increased the risk of ventricular fibrillation due to increased catecholamines Still we do not exercise patients immediately prior to coronary arteriography after this experience Ventricular fibrillation has not occurred in the last 197 consecutive examina tions

Vagal slowing of the heart is a common occur rence during coronary arteriography[13] Severe and prolonged bradycardia may delay the clearance of the contrast agent from the coronary artery with resultant myocardial hypoxia and ventricular arrhythmia Atropine has been useful in at least partially reducing the vagal response to coronary artery injections It has been shown recently that patients with two and three vessel disease are unable to increase myocardial blood flow in response to atropine induced cardioacceleration to the same degree as patients without coronary artery disease[14] This observation implies that in patients with significant coronary artery disease atropine may induce myocardial ischemia We have not observed chest pain ECG changes or cardiac arrhythmia induced by atropine in any of our patients When atropine fails to accelerate the heart rate cardiac pacing is necessary Petch Sutton and Jefferson[8] have reported four cases of vasovagal collapse possibly due to manipulation

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tions Of course the meticulous and expeditious performance of the procedure is the most important factor in reducing thromboembolic complications The theoretical possibility of increased coagulability of blood due to protamine may be hazardous in patients with severe coronary artery disease Also inadvertent vascular or cardiac perforation can occur during cardiac catheterization and may lead to a fatal hemorrhage in the presence of systemic heparinization In our experience the use of separate femoral arteries and continuous pressure drip of heparinized saline have been satisfactory in keeping the incidence of thromboembolic complications low

The very simplicity of the Judkins technique is likely to encourage neglect of minor details of the procedure which must be stringently observed to minimize all complications Although heparinization has been shown to reduce the incidence of thromboembolic complication it should not create an excessive sense of security to the point that the finer aspects of the technique be neglected We believe that the present paper adds some further precautions which reduce the risks of the procedure

Summary

Complications encountered during 351 selective coronary artery and coronary artery bypass examinations performed by the Judkins technique are reviewed The over all incidence of cardiac and peripheral vascular complications was 3 13 per cent The cardiac complications included four ventricular fibrillations and one acute myocardial infarction Peripheral vascular complications included three femoral artery thromboses, two peripheral emboli and one probable cerebral embolus There was one death The incidence of cardiac complications was not significantly different from that reported in the literature with the Sones technique and local arterial complications were significantly lower than those reported with the Sones technique The causes of individual complications are analyzed and measures to minimize these complications are described The Judkins technique is a simple reliable, quick and safe method of selective coronary arteriography The incidence of complications can be kept at an acceptably low level by stringent observation of every minor detail of the technique

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including one transplant rejection) and renovascular (two)

Sixteen patients had a documented history of one or more episodes of malignant hypertension in the past The duration of hypertension varied from < 1 to 10 years (mean 4 3) and the great majority were taking three antihypertensive drugs in addition to diuretics at the onset of minoxidil therapy In the majority minoxidil was begun because of lack of control on other drugs Eight patients were on dialysis at the initiation of therapy three had had sympathectomies one had had an insertion of a baropacer [1] and three had had bilateral nephrectomies performed in an unsuccessful attempt to control their pressures These three anephric patients remained hypertensive in spite of dialysis three times weekly with control of fluid balance

Historically congestive heart failure (CHF) was the most common cardiovascular complication present in the group Ten patients had a previous history of congestive heart failure and three additional patients had been admitted with their first episode of heart failure at the time minoxidil was begun Angina pectoris was distinctly uncommon with only two patients giving such a history One patient had had a myocardial infarction documented by serial ECG and enzyme changes A number of central nervous system events had occurred including encephalopathy (3) subarachnoid hemorrhage (1) thrombotic stroke (1) and generalized seizures (3)

A prior history of renal disease including glomerulonephritis and pyelonephritis was elicited in six

Table II shows the initial and follow up blood pressures The predrug pressures represent a mean of the pressures obtained while receiving other drug regimens for a week prior to initiation of minoxidil the follow up pressures reflect the most current outpatient readings or in certain instances in hospital pressures if the drug was discontinued prior to discharge The preminoxidil pressures averaged 202/127 mm Hg in the supine position and 162/106 upright During treatment with minoxidil pressures for the group averaged 154/87 supine and 143/86 upright

The dose range of minoxidil necessary to accomplish these substantial reductions in blood pressure varied from 2 0 to 40 mg per day (mean 23.2) At the initiation of therapy the drug was administered at a dose of 1 mg twice daily and was increased daily by doubling the amount given on the preceding day in two divided doses Excessive reduction of blood pressure was not seen when the drug was given in this manner Although most patients required more than 20 mg per day for good control the fact that some patients exhibited dramatic reduction with less than 10 mg per day necessitated that the dose be initiated at this low level Concomitant drug therapy was given to all patients except one as outlined in Table III

Most patients were receiving methyldopa and/or guanethidine at the time minoxidil was begun and in most cases the doses were decreased as blood pressure came under control In certain instances these drugs were subsequently discontinued, often due to patient preference and propranolol was begun In nine cases methyldopa alone was used to control reflex tachycardia and it functioned well. In four patients blood pressure control was just short of ideal on minoxidil and propranolol and in these instances a small additional dose of methyldopa (750 to 1 000 mg per day) proved to be very effective in providing the additional blood pressure reduction desired

Diuretic therapy was necessary in all patients not on dialysis Although in our hands minoxidil continued to be effective despite expansion of the extracellular volume the attendant edema and in some cases the precipitation of congestive heart failure necessitated use of diuretics In only one patient was a thiazide diuretic sufficient to alleviate the fluid retention In the 16 patients requiring furosemide the dose ranged from 80 to 1,200 mg per day (mean 350) Despite these large doses of potent diuretics edema and heart failure often persisted although usually of a degree tolerable to the patient Two patients had intractable edema and congestive heart failure despite extremely large doses of furosemide although the heart failure became predominantly right sided as opposed to mostly left sided prior to minoxidil.

Serial laboratory studies were obtained on all patients. Table IV outlines initial and follow up indices of renal function Excluding those patients on dialysis when minoxidil was initiated the BUN and creatinine showed little change with the exception of Patients 3 6 and 15 In Patients 3 and 6 the serum creatinines were 9 5 and 8 3 mg per 100 ml respectively prior to therapy with simultaneous creatinine clearances

Minoxidil in severe hypertension Value when conventional drugs have failed

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In spite of the development of an armamentarium of potent and generally effective antihypertensive drugs there remains a group of patients whose blood pressure for a variety of reasons, cannot be controlled These patients include those (1) refractory to maximum doses of conventional agents (2) with intolerable side effects with or without adequate pressure control, (3) showing progressively declining renal function despite fair control, and (4) on chronic hemodialysis All these difficult therapeutic problems have been encountered in the past 24 months and effectively managed with rare side effects with the new antihypertensive vasodilating drug, minoxidil Although not a controlled study our experience with minoxidil indicates not only its usefulness but also some of the problems with its use in hypertensive patients who have been heretofore inadequately controlled

Methods

A total of 26 patients with severe hypertension form the basis of this report These patients were selected by criteria outlined by an FDA approved emergency use' protocol, requiring patients to have life threatening hypertension refractory to conventional agents and/or associated with disabling side effects All patients had had a complete hypertensive evaluation including renal arteriography and renal vein renins when indicated Informed consent was obtained prior to initiation of therapy with minoxidil, which was always begun while patients were hospitalized

Pretherapeutic studies included complete blood count and platelet count, sedimentation rate, urinalysis electrolytes, blood urea nitrogen (BUN) and creatinine, creatinine clearance, urinary steroids vanillylmandelic acid (VMA) and catecholamines plasma renin activity (ambulatory) electrocardiogram (ECG), and chest x ray The blood studies were repeated at no less than 3 month intervals and more often if indicated

Concomitant drug therapy was handled individually In general methyldopa, guanethidine, and propranolol were continued at the preminoxidil level and hydralazine was discontinued If methyldopa or guanethidine were decreased or discontinued, propranolol was added to block reflex tachycardia[1] Blood pressures in the supine and standing positions and pulses were assessed four times daily during the patient s hospitalization and an average of two to three readings taken during each outpatient visit The patients were followed in the Hypertension Clinic following discharge

Results

Table I enumerates certain demographic and historical characteristics of the patient population In all 26 patients have received minoxidil since March, 1972 The patients varied in age from 20 to 57 years (mean 38) 18 were male and eight were female, 14 were white and 12 were black. Various etiologies for the hypertension existed including essential (17), renal (seven,

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History		*Recent History*			
CVA‡	*Renal disease*	*CHF*	*Angina*	*CVA‡*	*Renal disease*
		+		E	
	+				
E		+			
				SE	
E		+			
		+			
S		+		SE	
	+				+
		+			
			+		
		+			
	+	+			
		+			
SH					
	+				
	+				
		+			
	+			SE	
4	6	10	1	4	1

ography was normal A renal arteriogram was normal She returned 3 months later with headache nausea and vomiting and a blood pressure of 250/150 Xanthochromic spinal fluid was found Due to poor blood pressure control a total cervicothoracolumbar sympathectomy was performed A year later she presented with pulmonary edema a blood pressure of 260/?10 and reduced renal function

She entered Vanderbilt *Hospital* for the first time in November 1973 for further evaluation of her hypertension On admission she was taking digoxin (0 25 mg per day) methyldopa (500 mg three times a day) and reserpine (0 25 mg per day) She had previously been on guanethidine and large doses of methyldopa which gave severe orthostatic symptoms without supine pressure control. A trial of propranolol in the past had also failed Physical examination revealed a blood pressure of 260/134 supine and 120/95 upright without pulse change The fundi revealed hemorrhages and exudates. The point of maximal impulse (PMI) was displaced toward the axilla in the fifth intercostal space the lungs were clear there was a trace of peripheral edema

She was brought into 10 mEq sodium balance and therapeutic trial of hydralazine up to ?00 mg per day was given As shown in Fig 1 there was no change in the pressure with this maneuver She did, however develop headaches on this regimen which continued after minoxidil was instituted Propranolol was begun on Nov 26 and there was a prompt fall in the blood pressure accompanied by a resolution of the headaches The plasma renin activity (PRA) also fell strikingly after the institution of propranolol

Because of the unique surgical procedure in this patient with interruption of the sympathetic efferents to the heart it was felt that propranolol was probably exerting its hypotensive effect through suppression of renin rather than by cardiac beta adrenergic blockade To test this hypothesis, a propranolol placebo was substituted on Dec 3 with a rise in blood pressure within 6 to 12 hours. As can be seen the plasma propranolol level fell from 223 to 11 ng per milliliter in 24 hours, associated with a rise in the upright PRA from 7.5 to 29 5 ng of angiotensin I per milliliter per hour along with the rise in blood pressure but with no change in heart rate Following reinstitution of propranolol and resultant increased plasma propranolol levels the PRA fell to 5 4 and the blood pressure returned to its previous level Withdrawal of minoxidil also resulted in loss of pressure control At the time of discharge her supine and upright blood pressures were equal and she was sent home on minoxidil (30 mg per day) propranolol (160 mg per day) and furosemide (80 mg per day)

Comment This young woman presented with a history of life threatening cardiovascular complications and refractory hypertension despite heroic measures The sympathectomy acted to exaggerate the orthostatic effect of sympathetic inhibiting drugs but left her with severely elevated supine pressures Minoxidil combined with propranolol was able to control both supine and upright pressures Although not supported by cardiac output studies the fact that the heart rate was constant due to interruption of the cervical sympathetics suggests that *the additional* effect of propranolol on blood pressure was mediated through suppression of renin release[3] Patients 7 and 14 also had had previous thoracolumbar sympathectomies without sufficient reduction in blood pressure In both these cases pressure was controlled with minoxidil

Use in far advanced renal failure

Case 13 This 44 year old black man first presented to Vanderbilt Hospital in February 1972 with malignant hypertension (blood pressure 230/140 mm Hg) a BUN of 50 mg per 100 ml., and creatinine clearance of 20 c c per minute no remediable cause for the hypertension was found He was treated with guanethidine hydralazine propranolol and furosemide, *with poor control* of both supine and upright pressures. Over the next 8 months the BUN and creatinine rose to 87 and 9.2 mg per 100 ml., respectively and the creatinine clearance fell to 9 c c per minute He had also developed signs and symptoms of congestive heart failure at that time

Hydralazine was discontinued and minoxidil was instituted

Table I Demographic and historical characteristics of patient population

Patient	Age (yr)	Sex	Race	Etiology*	Duration of hypertension (yr)	History of malignant hypertension	Dialysis/nephrectomy	No of antihypertensive drugs at onset	Reason to begin minoxidil†	Remote	
										CHF	Angina
1 L T	45	M	B	E	6		+/−	3	C	+	
2 F C	43	F	B	R	0 5	+	+/−	2	C S		
3 A H	37	M	B	R	9	+	+/−	2	C S		
4 F C	45	F	B	E	8		+/−	3	S	+	
5 M B	37	M	W	F	2	+		3	C		
6 W H	42	M	B	E	6	+		3	C	+	
7 G D	43	F	B	F	3	+		3	C	+	+
8 H Y	52	M	W	E	7	+		3	C	+	
9 T M	33	F	W	R	0 5	+	+/−	3	C	+	
10 B D	20	M	W	TR	0 5			3	C		
11 F D	46	F	W	F	1			4	C	+	
12 C W	51	M	W	R V	10	+		3	C		
13 W M	43	M	B	E	4	+		3	C		
14 W P	25	M	W	F	5	+		3	C		
15 P J	20	F	W	R	1	+	+/+	3	C S		
16 W H	38	M	W	F	6			2	C	+	
17 W C	30	F	W	F	4			3	C S	+	
18 H N	57	M	W	R V	2 5			3	C S		
19 B D	20	M	W	R	Unk		+/+	2	C		
20 B T	24	M	B	E	6	+		3	C		
21 W M	33	M	B	E	10	+		3	C		
22 J S	21	M	B	E	3	+		2	C		
23 P H	20	F	W	R	1.5	+	+/+	2	C		
24 G D	51	M	B	E	3			3	C		
25 J A	57	M	W	E	5			3	C		
26 A C	57	M	W	E	3	+		2	C		
Mean	38				4 3					9	1

*E Essential R renal R V renovascular TR transplant rejection
† C control failure S side effects of other drugs
‡CVA ~ cerebrovascular accident E encephalopathy SH subarachnoid hemorrhage S thrombotic stroke SE seizure

of 10 and 11 c c per minute Patient 3 died after 3 months of therapy despite considerable reduction in his pressure whereas Patient 6 came to dialysis with subsequent nephrectomy after 8 months of therapy due to intractable heart failure and anasarca despite good blood pressure control Thus, although the mean pretreatment creatinine was elevated vigorous antihypertensive therapy did not lead to reduction in renal function in most patients

Minoxidil was discontinued in 10 patients after a period of therapy ranging in duration from 1 to 10 months In none was the drug discontinued because of ineffectiveness Four patients had nephrectomy early in the study and no longer required minoxidil, in one dialysis was discontinued, and in one the blood pressure became easier to control while in the hospital and the minoxidil was no longer required Two patients died after 3 months of therapy Two patients had the drug stopped because of refractory edema and congestive heart failure Of the 17 patients still on the drug the duration of therapy has varied from 4 to 19 months (mean 7)

Selected case reports follow which emphasize some unique features of the patient population and the usefulness of minoxidil in difficult therapeutic situations

Use in refractory hypertension with prior sympathectomy

Case 17 This 30 year old white woman developed hypertension 3½ years prior to beginning minoxidil She was initially hospitalized elsewhere with severe headaches grade 2 hypertensive retinopathy and a blood pressure of 160/120 mm Hg. Electroencephalogram (EEG) and brain scan suggested a right sided abnormality right carotid arteri

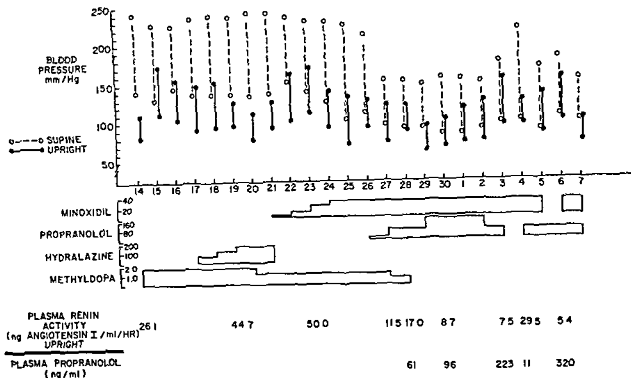


Fig 1 Blood pressure drug usage plasma renin activity and plasma propranolol levels in case 17 illustrating the additive hypotensive effect of propranolol. Drug doses are in milligrams except for methyldopa, which is in grams. See text for discussion.

Comment Transplant rejection hypertension responded well to minoxidil therapy in this case

Refractory edema

Case 20 B T., a 24 year-old black man presented to Vanderbilt Hospital with a 1½ year history of recurrent episodes of acute pulmonary edema and malignant hypertension. He had received a variety of antihypertensives without control including propranolol hydralazine methyldopa guanethidine and furosemide On arrival he was taking guanethidine (300 mg per day) and furosemide (240 mg a day) At that time he had a blood pressure of 190/120 supine and 160/110 upright. The fundi showed hemorrhages and exudates. Findings of congestive heart failure were present. The BUN was 36 mg per 100 ml., creatinine 4 5 mg per 100 ml., and creatinine clearance 17 c c per minute Guanethidine was discontinued and minoxidil begun and quickly increased to 40 mg per day Propranolol was begun at 120 mg per day and furosemide 80 mg. per day At discharge the blood pressure was 180/106 supine and 168/86 upright He weighed 190 pounds.

As an outpatient, he rapidly gained approximately 45 pounds of weight. In contrast to multiple previous admissions, the fluid accumulation did not lead to acute pulmonary edema but rather was manifested by anasarca despite furosemide doses of 400 mg twice daily and continued fair control of blood pressure In February 1974 he was readmitted with a weight of 235 blood pressure of 200/130 and findings of severe right heart failure At that time the BUN was 58 creatinine 6.2, and creatinine clearance 18 c.c. per minute A 10 mEq sodium diet was given and all the medications were continued. Because of the problems with recurrent congestive heart failure and anasarca despite high doses of furosemide right heart catheterization was performed to assess cardiac function. Findings showed a pulmonary artery pressure of 70/30 (mean, 45) with a mean pulmonary capillary wedge pressure of 12 and a left ventricular pressure of 135/6-14 The cardiac output was 11 1 L. per minute per square meter with a cardiac index of 5.5 L. per minute per square meter Thus, despite propranolol therapy sufficient to control the cardiac rate the cardiac output was elevated during minoxidil therapy Calculated pulmonary vascular resistance was 238 dyne/sec /cm which was at the upper limit of normal.

Comment This patient and Patients 8 and 9 are the three examples in this series of patients with moderately advanced renal insufficiency who had problems with fluid retention refractory to very large doses of furosemide Why these patients had so much difficulty and yet Patients 16 and 22 with more advanced renal failure did not manifest this problem is unknown The hypothesis that pulmonary hypertension could cause the right heart failure remains a possibility

Table II Blood pressure and pulse responses to minoxidil

Patient	Predrug*		Minoxidil†		Pulses‡	
	Supine	Upright	Supine	Upright	Supine	Upright
1 L T	220/120	180/100	205/115	180/100	96	§
2 F C	200/120	180/110	150/90	130/80	§	§
3 A H	270/142	190/125	146/102	160/112	88	§
4 E C	190/132		154/96			§
5 M B	180/135	150/115	130/90	120/85	§	§
6 W H	225/115	200/110	193/102	158/90	92	§
7 G D	200/120	130/90	160/90	128/90	74	§
8 H Y	225/137	170/115	196/104	214/100	96	§
9 T M	189/116	128/96	180/80		80	84
10 B D	162/112	173/63	135/90	110/70	80	80
11 F D	220/120	100/70	164/96	150/94	96	84
12 C W	217/132	162/112	154/70	160/70	76	84
13 W M	190/135	180/125	140/80	140/76	88	100
14 W P	220/140	134/100	140/88	118/80	68	64
15 P J	240/160		132/60	150/70	84	96
16 W H	200/130	180/110	120/80	136/80	84	88
17 W C	240/140	120/80	178/80	180/90	64	68
18 H N	200/120	160/110	166/80	136/84	88	88
19 B D	170/130		130/88	114/88	72	84
20 B T	190/120	160/110	160/98	140/96	80	88
21 W M	180/120	190/140	170/120	152/120	96	100
22 J S	170/110	160/110	170/70	140/84	88	100
23 P H	165/105		158/64	150/68	88	84
24 G D	220/120	120/80	120/90	120/78	108	108
25 J A	230/136	194/128	122/70	120/76	68	68
26 A C	210/160	210/146	126/80	122/82	88	88
					88	84
Average	202/127	162/106	154/87	143/86		

*Mean values for week prior to onset of therapy
†Average of most recently determined outpatient values or at time of discontinuation
‡Outpatient
§Not available

at this point at a dose of 2 0 mg per day and gradually increased to 30 mg per day with continuation of the guanethidine (75 mg per day) propranolol (240 mg per day) and furosemide (160 to 240 mg. per day) On this regimen the blood pressure came under very good control in both the supine and upright positions Eighteen months later dialysis was necessary because of edema refractory to 1 200 mg of furosemide per day At that time the blood pressure was 140/72 supine and 128/70 upright The BUN and creatinine were 92 and 10 0 mg per 100 ml respectively

Comment This case emphasizes the potential of effective antihypertensive therapy to delay dialysis for considerable periods Despite end stage renal function this man went more than 18 months before dialysis was required As can be seen from Table IV, several other patients began the drug with serum creatinines greater than 5 mg per 100 ml and remain in that range without dialysis

Transplant rejection

Case 10 B D a 20 year old white man received a renal transplant in August 1972 and did well except for mild rejection controlled with increased doses of immunosuppressives In the fall of 1973 however he presented with 3+ proteinuria a BUN of 82 and a blood pressure of 170/100 The blood pressure gradually increased and by Dec 1 1973 it had risen to 190/140 He was begun on increasing doses of methyl dopa hydralazine propranolol and a diuretic without normalization of blood pressure Minoxidil was begun and increased to 15 mg per day with blood pressure falling to 120/75 supine and 110/80 upright He was discharged on minoxidil (15 mg per day) propranolol (160 mg per day) and furosemide (120 mg per day)

His blood pressure at home and in the outpatient clinic remained less than 140/90 supine and upright In February 1974 however he presented with hemoptysis congestive heart failure and rapidly deteriorating renal function despite completely normal blood pressures Because of graft failure a transplant nephrectomy was required Postoperatively the blood pressure normalized with the patient taking no medication

because of intolerable side effects from other drugs that precluded successful normalization of blood pressure Severe orthostatic hypotension was a frequent problem prior to minoxidil as illustrated in case 17 Vasodilators are particularly advantageous in this circumstance as sympathetic reflexes are maintained and good control is accomplished in both supine and upright positions[10] Hemodialysis often presents a therapeutic problem Because of the volume changes that occur patients on sympathetic blocking drugs not infrequently exhibit hypotension during and immediately after dialysis If the dose of drug is diminished to avoid this problem an unacceptable degree of hypertension is often present by the time of the next dialysis Patients in our series both with and without nephrectomy had good control of blood pressure with minoxidil despite the fluid changes Similar findings have been reported by Limas and Freis[7]

The dosage required for response varied from 2 0 to 40 mg per day Although some aspects of the metabolic fate of minoxidil are known[11] the lack of a sensitive assay of the parent compound and its metabolites in plasma and urine makes generally applicable pharmacokinetic principles unreliable at this time and the dose for the individual patient must be determined empirically

Essentially all patients on minoxidil required concomitant drug therapy to block the reflex cardiac effects of the vasodilator and propranolol methyldopa or guanethidine all were adequate Orthostatic hypotension was less of a problem with propranolol however and hence the preference for propranolol in many patients Additionally the ability of propranolol to suppress minoxidil induced renin rise may be as important as the prevention of reflex cardiac effects Our Patient 17 who had a surgical sympathectomy did not develop a reflex tachycardia but propranolol still gave an additional hypotensive effect associated with suppression of plasma renin activity Four patients on propranolol minoxidil and diuretic required the addition of 750 to 1 000 mg per day of methyldopa before blood pressure control was achieved This occurred without further change in heart rate and made pressure control possible for the first time in these patients

Drug related side effects of minoxidil were uncommon There was no instance of development of a positive LE prep or antinuclear antibody as has been associated with another vasodilator hydralazine[12] Hypertrichosis however did occur as a result of minoxidil This consisted of hair growth most noticeable on the face particularly the temples but increased on the arms and at times on the chest and back. The generalized growth was most evident in two young females on dialysis but it did not necessitate discontinuation of the drug

The problem that created the most difficulty in the series was the edema associated with minoxidil use The excessive retention of salt and water eventually led to discontinuation of the drug in two of our patients and to dialysis in another although the blood pressure was well controlled These patients did have markedly impaired renal function and failed to respond to gradually increasing doses of furosemide up to 1,200 mg per day Discontinuing the drug was associated with lessening of the edema and heart failure but a

Table IV BUN and creatinine responses of patients not on dialysis obtained prior to onset of minoxidil therapy and at the most recent follow up

	BUN		Creatinine	
Patient	Before	After	Before	After
1				
2	94	†	12.6	†
3	116	195	9.5	16 5
4				
5	52	62	4.5	5 8
6	90	†	8 1	†
7	100	†	11 6	†
8	41	125	4 4	10 0
9				
10	54	120	2.6	10 5
11	63	51	3 6	3 4
12	13	18	1 7	2 0
13	87	9?	9 2	> 10
14	13	16	1 6	1 7
15				
16	55	59	6 8	7.3
17	32	32	3 0	2 1
18	38	30	2 0	2 0
19				
20	36	58	5 5	6.2
21	21	16	1.2	1.3
22	44	60	5 3	5 9
23				
24	25	24	2.1	2.2
25	39	44	4.2	3 9
26	68	44	4 3	3 6

On dialysis at time beginning minoxidil.
†Began dialysis after initiation of minoxidil

Table III Minoxidil use and concomitant drug therapy in patient population

Patient	On therapy (mo)	Reason to discontinue	Doses of drugs (mg/day)				
			Minoxidil	Propranolol	Methyldopa	Guanethidine	Furosemide
1	1	N	15		1 500	100	D†
2	3	N	30		2 000		D†
3	3	D	7 5	240	2 000	75	160
4	< 1	F	40		1 000		D†
5	< 1	C	2 5	80	7_0	25	80
6	8	N	30		1 000	25	800
7	3	S	30		750		800
8	11	S	30		1 _00		1,200
9	_	D	20	80			D†
10	4	N	15	240			120
11	13		30	480			120
12	11		25		2 000		40
13	19		3_	60			800
14	15		40	480			160
15	13		2		1 000		D†
16	5		40	80	750		240
17	5		35	160			160
18	7		20	160	1,500		‡
19	8		10				D†
20	7		40	320	1 000		800
21	4		10	80	2 000	100	160
22	7		20	320			160
23	8		5	80			D†
24	5		15	800		30	160
25	7		20	160	1 000		200
26	8		40	320			120
Mean	7		23 3				350

N Nephrectomy C controlled on other drugs D died S side effect (heart failure) F encephalopathy not a dialysis candidate
†D Dialysis
‡Hydrochlorothiazide 50 mg

Patient 8 had a right heart catheterization showing a mean pulmonary artery pressure of 45 mm Hg and a mean pulmonary capillary wedge pressure of 14 mm Hg Cardiac output was not determined and pulmonary vascular resistance could not be calculated

Discussion

Severe hypertension continues to be a difficult therapeutic problem despite a number of useful antihypertensive agents When hypotensive therapy is effective, particularly in patients with severe hypertension, prognosis is improved,[4] but when a patient presents with refractoriness to the usual agents the prognosis is poor

The patients in this study represent a wide spectrum of problems in antihypertensive therapy The most common reason for initiation of minoxidil therapy was that of failure to adequately control the blood pressure That this was no ordinary group of patients is evidenced by the heroic methods used prior to minoxidil to obtain blood pressure control including surgical sympathectomies carotid baropacing, all conventional drugs, and bilateral nephrectomy Nonetheless excellent results were seen in this group of patients which compare favorably with those published previously[5,8] Despite rapidly deteriorating renal function in many of these patients, adequate control with minoxidil stabilized renal function and forestalled nephrectomy and dialysis

Severe hypertension is associated with rejection episodes of renal transplantation[9] In this setting blood pressure control is difficult due to the renal abnormality and the high doses of corticosteroids used However normotension is desirable not only for the general cardiovascular system but also to limit injury to the affected kidney Minoxidil proved itself to be efficacious in this instance (case 10)

Several patients were treated with minoxidil

because of intolerable side effects from other drugs that precluded successful normalization of blood pressure Severe orthostatic hypotension was a frequent problem prior to minoxidil as illustrated in case 17 Vasodilators are particularly advantageous in this circumstance as sympathetic reflexes are maintained and good control is accomplished in both supine and upright positions[10] Hemodialysis often presents a therapeutic problem Because of the volume changes that occur, patients on sympathetic blocking drugs not infrequently exhibit hypotension during and immediately after dialysis If the dose of drug is diminished to avoid this problem an unacceptable degree of hypertension is often present by the time of the next dialysis Patients in our series both with and without nephrectomy had good control of blood pressure with minoxidil despite the fluid changes Similar findings have been reported by Limas and Freis[7]

The dosage required for response varied from 2 0 to 40 mg per day Although some aspects of the metabolic fate of minoxidil are known [1] the lack of a sensitive assay of the parent compound and its metabolites in plasma and urine makes generally applicable pharmacokinetic principles unreliable at this time and the dose for the individual patient must be determined empirically

Essentially all patients on minoxidil required concomitant drug therapy to block the reflex cardiac effects of the vasodilator and propranolol methyldopa or guanethidine all were adequate Orthostatic hypotension was less of a problem with propranolol however and hence the preference for propranolol in many patients Additionally the ability of propranolol to suppress minoxidil induced renin rise may be as important as the prevention of reflex cardiac effects Our Patient 17 who had a surgical sympathectomy did not develop a reflex tachycardia but propranolol still gave an additional hypotensive effect associated with suppression of plasma renin activity Four patients on propranolol minoxidil and diuretic required the addition of 750 to 1 000 mg per day of methyldopa before blood pressure control was achieved This occurred without further change in heart rate and made pressure control possible for the first time in these patients

Drug related side effects of minoxidil were uncommon There was no instance of development of a positive LE prep or antinuclear anti

Table IV BUN and creatinine responses of patients not on dialysis obtained prior to onset of minoxidil therapy and at the most recent follow up

Patient	BUN		Creatinine	
	Before	*After*	*Before*	*After*
1				
2	94	†	12.6	†
3	116	195	9.5	16.5
4				
5	52	62	4.5	5.8
6	90	†	8 1	†
7	100	†	11 6	†
8	41	125	4 4	10 0
9				
10	54	120	2 6	10 5
11	63	51	3 6	3 4
12	13	18	1 7	2.0
13	87	92	9.2	> 10
14	13	16	1 6	1 7
15				
16	55	59	6 8	7.3
17	3?	32	3 0	2 1
18	38	30	2 0	2 0
19				
20	36	58	5 5	6.2
21	21	16	1 2	1.3
22	44	60	5.3	5.9
23				
24	25	24	2 1	2.2
25	39	44	4 2	3 9
26	68	44	4.3	3 6

On dialysis at time beginning minoxidil.
†Began dialysis after initiation of minoxidil.

body as has been associated with another vasodilator hydralazine[1] Hypertrichosis however did occur as a result of minoxidil This consisted of hair growth most noticeable on the face particularly the temples but increased on the arms and at times on the chest and back The generalized growth was most evident in two young females on dialysis but it did not necessitate discontinuation of the drug

The problem that created the most difficulty in the series was the edema associated with minoxidil use The excessive retention of salt and water eventually led to discontinuation of the drug in two of our patients and to dialysis in another although the blood pressure was well controlled These patients did have markedly impaired renal function and failed to respond to gradually increasing doses of furosemide up to 1,200 mg per day Discontinuing the drug was associated with lessening of the edema and heart failure but a

return of hypertension This problem has apparently not been encountered in the previously published clinical studies with minoxidil and may reflect the very severe hypertensive cardiovascular disease present in our patients with the associated renal failure

The mechanism underlying the salt retention and right heart failure remains unclear Humphrey and associates,[13,14] using radioactively labeled microspheres, found that renal blood flow was not changed following administration of minoxidil to the conscious dog although a shift of blood flow to the juxtamedullary cortex did occur in association with increased proximal tubular sodium reabsorption Another possibility, suggested by our observations, is that pulmonary hypertension may develop in some patients on minoxidil and propranolol, resulting in right heart failure Requiring further study are the incidence of pulmonary hypertension in hypertensive patients the mechanism of its occurrence, the relationship to antihypertensive drug therapy, and the reversibility of the abnormality

In summary, minoxidil has been shown to be potent and effective in patients with refractory hypertension of varying etiologies when combined with a diuretic and a sympathetic inhibiting drug In some patients with renal failure, fluid retention occurs and is difficult to manage Nonetheless our experience and that of others indicates that minoxidil is a drug worthy of further study since it offers hope for the control of hypertension which is refractory to other drugs

Summary

Twenty six patients were selected for treatment with minoxidil on the basis of hypertension which could not be controlled either because of (1) drug failures and/or (2) side effects of drugs Sixteen out of the 26 had had one or more previous episodes of malignant hypertension Reduced renal function was present in the majority, eight patients were on dialysis Average pre minoxidil blood pressure was 202/127 mm Hg supine and 162/106 upright which fell to 154/87 supine and 143/86 upright after minoxidil Propranolol or methyldopa was given to control the reflex increase in heart rate Edema and congestive heart failure refractory to large doses of potent diuretics necessitated discontinuation of the drug in two patients Minoxidil proved highly efficacious regardless of initial level of blood pressure, etiology, or supine or upright posture

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Case reports

Paroxysmal hypertension in aortitis syndrome

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Aortitis syndrome (Takayasu s arteritis) is characterized by stenotic inflammatory lesions of the aorta and its large branches affecting mainly young women[1,2] The pathogenesis of the inflammation is still unknown although an autoimmune mechanism is thought to be responsible Sustained hypertension is a frequent complication of this disease as reported by many authors[3]

The mechanism of such hypertension in aortitis syndrome is complex but may be summarized in five categories[7,8] (1) the mechanical factor increased blood flow to the unaffected vessels due to shifts away from stenotic inflamed vessels atypical coarctation of the aorta [9] and reduced elasticity of the arterial wind kettle (2) decreased cerebral blood flow (3) disruption of the baroreceptors (4) reduced renal blood flow[1 3] and (5) aortic regurgitation due to *inflammatory destruction of the medial elastic* fibers of the aorta[1] These types of hypertension persist when appropriate treatment is not given

Involvement of the aortic arch and the carotid arteries including the baroreceptors is common in this disease and such lesions are thought to be responsible for the sustained hypertension and for hypotension seen with external carotid sinus compression [7] It has not been widely recognized however that some patients with aortitis syndrome exhibit paroxysmal hypertension We are reporting three such cases one has been described previously in Japanese[13] This report of paroxysmal hypertension and tachycardia associated with aortitis syndrome strongly suggests impaired baroreceptor function

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Case reports

Patient 1 I T A 38-year-old Japanese woman who had a weak left radial pulse and occasional high fever with arthralgia of the knees since the age of 30 was admitted to the Kagoshima University Hospital on Nov 10 1965 About one year prior to admission bilateral pulsating neck tumors slight hypertension and proteinuria were noticed At the same time she developed easy fatigability exertional palpitation and dyspnea precordial oppression and frequent attacks of dizziness with severe headache Sharp pains in the lower limbs back and neck were frequently experienced Six months before admission she began to have peculiar attacks of hypertension which were preceded by severe headache and palpitation and followed by precordial pain and flushing of the face There were no noticeable precipitating factors and the attacks subsided spontaneously in a few hours

On physical examination her left radial pulse was feeble *and a small pulsating tumor was detected in the region of the* right common carotid artery The carotid arteries were tender bilaterally on palpation Pulse was 72 beats per minute and regular The blood pressure was 154/40 mm Hg in the right arm 90/70 in the left arm and 168/40 in the lower limbs A rough systolic murmur of grade 4 was heard over the upper part of the chest supraclavicular area both sides of the neck and in the back A soft diastolic murmur was heard at the aortic area and radiated to the apex There were no abdominal bruits Chest x ray films disclosed dilation of the aortic silhouette and normal cardiac size The electrocardiogram revealed evident ST depression and inverted or diphasic T waves with findings of left ventricular hypertrophy as shown in Fig 1 *A* Angiocardiography clearly visualized the enlarged ascending aorta *stenotic* and indistinct subclavian and common carotid arteries. Aneurysms in the right brachiocephalic artery and right common carotid artery were also outlined Retrograde aortography revealed uneven aortic wall and normal renal arteries Carotid sinus massage resulted in a

The case of Patient 1 was outlined t the tw ntieth Kyu h R g on l Meeting of the J panese C culation Society J n 1966

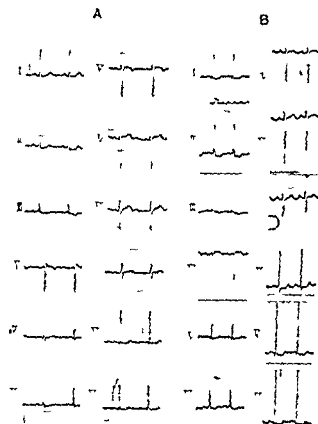


Fig 1 Electrocardiogram of Patient 1 taken at rest (*A*) and at the time of hypertensive attack (*B*) Note the aggravated ST depression and elevation of the amplitudes of QRS complexes in the left precordial leads during an attack

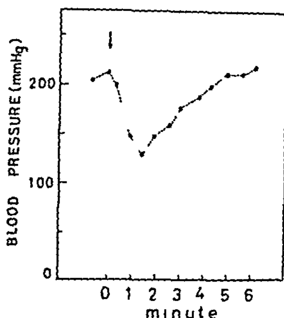


Fig 2 Effect of intravenous administration of phentolamine (*5 mg*) *in Patient 1 on the systolic blood pressure during an* attack of hypertension

systolic blood pressure fall of 46 mm Hg and a 28 beat per minute decrease in heart rate Accelerated erythrocyte sedimentation rate leukocytosis positive CRP test and increased γ globulin concentration were additional clinical findings (Table I) Such data suggested that this patient had active aortitis syndrome with associated aortic regurgitation During the attacks of paroxysmal hypertension the patient complained of increasing severe headache tinnitus palpitation and precordial oppression at these times the blood pressure was elevated to 230/50 mm Hg in the right arm and the pulse rose to 105 beats per minute She was slightly dyspneic and mydriatic An electrocardiogram taken at the time of an *attack showed marked elevation of the amplitudes of the QRS* complexes especially in the left precordial leads and aggravated ST depression as shown in Fig 1 *B* The elevated blood pressure rapidly returned to the usual level after intravenous injection of 5 mg of phentolamine as shown in Fig 2 However urinary catecholamines were always normal About 13 to 15 attacks were observed during the admission On the sixtieth hospital day oral administration of dexamethasone was started The signs and symptoms of active inflammation were rapidly suppressed and the frequency and severity of the attacks were considerably reduced The sympathetic ganglionic blocking agent hexamethonium was added on the eighty fifth hospital day The hypertensive attacks remitted during the time of its administration Afterward the attacks were completely prevented with dexamethasone therapy alone However vascular murmurs aortic regurgitation and occasional anginal pain on exertion showed poor improvement

Patient 2 K K On April 22 1971 a 22 year old Japanese woman with aortitis syndrome was sent to our university hospital for examination of aortic aneurysm aortic regurgitation and paroxysmal hypertension Since the age of 15 transient blurred vision followed by headache nausea and vomiting had occurred several times a year In 1967 at the age of 18 she developed fever sore throat and joint pains and the diagnosis of aortic regurgitation was made In 1968 she had her first attack of sudden palpitation severe headache and dyspnea followed by precordial pain choking sensations sweating and flushing of the face Increased blood pressure of 240/0 mm Hg and tachycardia of 136 beats per minute were observed during the attack The frequency and the severity of the attacks increased gradually and eventually occurred even during sleep Sublingual administration of 5 mg of isosorbide dinitrate promptly relieved the precordial pain and dyspnea However the hypertension and tachycardia lasted about 30 minutes or more Two months before admission she caught a cold and developed shortness of breath but was successfully treated with proscillaridin

On physical examination her left radial pulse was weak and the blood pressure was 120/30 mm Hg in the left arm 140/36 in the right arm and 140/0 in the lower limbs The cardiac dullness was distended to the left A grade 4 harsh systolic murmur was heard over the entire precordium most audible in the aortic area and in the carotid region An aortic regurgitant murmur was most prominent over the aortic area and radiated toward the apex There was no bruit on the abdominal aorta Carotid sinus massage caused a 10 mm Hg decrease of blood pressure and 10 beats per minute fall in pulse rate The thoracic aorta was remarkably enlarged as shown in Fig 4 and the cardiothoracic ratio was 65 per cent An electrocardiogram taken during a hypertensive attack disclosed marked elevation of QRS amplitudes and aggravation of the resting ST depression (Fig 3) Renal function tests and renogram revealed near normal values At this time aortitis was active (Table I) A markedly enlarged thoracic aorta and obscure common carotid and subclavian arteries were outlined

by an angiography performed in the right atrium as shown in Fig 4 The pulmonary truncus was also distended slightly Oral administration of beta methasone was begun on the twentieth hospital day The signs and symptoms of active inflammation were readily suppressed and the attacks of hypertension completely ceased in a short time However stenotic vascular murmurs and aortic regurgitation remained for a long time

Patient 3 Y M A 30-year old Japanese woman with aortitis syndrome was admitted to our university hospital on July 22 1968 with complaints of recurrent dizziness and headaches palpitation lassitude and visual disturbances which had begun five months before admission

Physical examination on admission revealed moderate anemia feeble left radial pulse and stenotic vascular murmurs and thrills bilaterally on the carotid arteries A slight systolic murmur was present at the apex but there was no bruit on the abdominal aorta The blood pressure was 110/56 mm Hg in the right arm 100/60 in the left arm and 96/60 in the lower extremities Slight bilateral choked discs and retinal edema and folds in the nasal side of the right optic disc were observed The arterial pressure in the fundus was apparently low and the visual acuity and the visual fields were also bilaterally impaired There were no neurologic signs suggesting spinal cord lesions Chest x ray films electrocardiograms and electroencephalograms disclosed near normal findings Retrograde aortography revealed an uneven aortic arch and brachiocephalic artery and stenotic common carotid arteries The presence of active inflammation of aortitis was evident (Table I) Oral administration of prednisolone started at the tenth hospital day brought about rapid improvement of ocular symptoms, anemia erythrocyte sedimentation rate and γ globulin concentration and her radial pulse became stronger

Eighteen days after the initiation of steroid therapy she had an attack of severe headache palpitation nausea and vomiting immediately after micturition At this time marked hypertension of ?30/96 mm Hg and tachycardia of 110 beats per minute were observed These returned gradually to the usual levels in three hours After this whenever she passed urine there was an immediate increase of blood pressure accompanied by tachycardia splitting headache sweating palpitation and flushing of the face The attacks were observed after voiding even in the recumbent position but the elevation of blood pressure and the heart rate after defecation was slight Although filling the bladder with water and its draining with an indwelling catheter did not elicit any hypertensive attacks, voluntary urination after irrigating the bladder provoked hypertension with tachycardia as shown in Fig 5 *B* and *C* Cystoscopic examination revealed a normal bladder mucosa Carotid sinus function was well preserved since carotid sinus massage yielded a systolic blood pressure fall of 40 mm Hg and complete A V block with sinus slowing and A V junctional escape Valsalva maneuver which resembled the strain initiating micturition produced an increase of systolic blood pressure of 80 mm Hg and tachycardia but these effects were significantly inhibited by simultaneous carotid sinus massage Provocative test for pheochromocytoma with histamine was negative Continuous treatment

P tient 3 was already reported by u 1 J pa ese as ind cated by reference 15

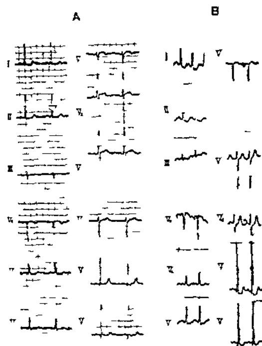


Fig 3 Electrocardiogram of Patient 2 taken at rest (*A*) and at the time of paroxysmal hypertension (*B*) Note marked ST depression and increased QRS amplitudes in the left precordial leads during an attack.



Fig 4 Angiocardiogram of Patient ? shows remarkable enlargement of the entire thoracic aorta and obscure common carotid and subclavian arteries.

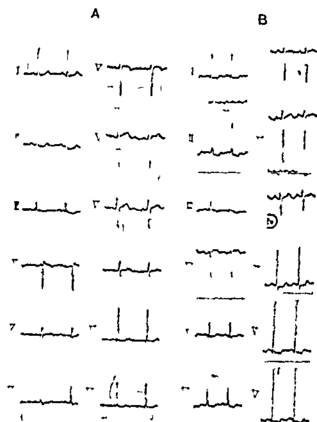


Fig 1 Electrocardiogram of Patient 1 taken at rest (*A*) and at the time of hypertensive attack (*B*) Note the aggravated ST depression and elevation of the amplitudes of QRS complexes in the left precordial leads during an attack

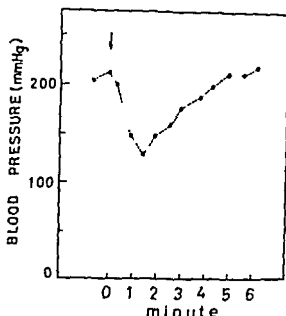


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this paper might be a specific type of neurogenic hypertension

In Patient 1 pheochromocytoma and glomus tumor [3] were strongly suspected since a positive phentolamine test and a pulsatile neck tumor were noted These were excluded however by normal urinary catecholamines and evident effect of steroid hormone on the attacks Phentolamine yields effective adrenergic blockade and blocks not only the elevation of blood pressure in pheochromocytoma but also the pressor response elicited by stimulation of the sympathetic nerves and the pressor response induced by the occlusion of common carotid arteries [25] Hexamethonium which sufficiently suppressed the attacks in Patient 1 provides an effective blockade of the sympathetic ganglia [2, 26]

The clinical symptoms and the effect of steroid hormone in Patient 2 closely resembled those in Patient 1 Both patients had not only hypertension but also tachycardia during attacks Therefore we considered that the paroxysmal hypertension in these patients might have been derived from the sympathicotonic state induced by the dysfunction of the baroreceptors For instance if the systemic blood pressure was slightly reduced their stenotic carotid arteries would have caused severe reduction of the carotid sinus pressure with a subsequent sympathicotonic state Localized pressure on carotid arteries such as flexion of the neck could provoke the same effects Besides the stenotic lesions might have interfered with the carotid sinus pressure responding to the raised systemic blood pressure resulting from the sympathicotonic state and prolonged the duration of hypertension and tachycardia Slight inflammatory impairment of the baroreceptor itself and inflammatory infiltration which stiffened the arterial wall around the baroreceptors were also presumed to elicit the hypertension when the systemic blood pressure was elevated Because such lesions would reduce sensitivity of the baroreceptors hypertension was allowed to persist Sudden aggravation followed by rapid recovery of the inflammation of the baroreceptors or of the stenotic carotid arteries was also thought to be able to produce paroxysmal hypertension The effect of steroid hormones on the attacks might be interpreted as the result of relief of inflammatory lesions of the carotid arteries or of the baroreceptors

As a rule during an attack of angina pectoris the blood pressure and the pulse rate do not change remarkably [34] On the other hand hypertension and tachycardia are apparent precipitating factors of angina pectoris and the electronic carotid stimulator recently introduced for the treatment of severe uncontrolled angina pectoris [30] and diastolic hypertension[22, 31] was reported to be very effective Therefore in our patients with aortic regurgitation the anginal pain and the electrocardiographic changes observed during attacks could be considered to be the result of hypertension and tachycardia Although the turnover rates of renin and angiotensin are relatively short [3, 33] renovascular mechanism was considered unlikely to have produced the paroxysmal hypertension with tachycardia lasting for only a few hours

It is difficult to understand the mechanism of post micturition hypertension in Patient 3 Pheochromocytoma especially in the bladder [35] and autonomic hyperreflexia associated with spinal cord lesions[16, 37] are also characterized by paroxysmal hypertension with voiding The former was ruled out by a negative histamine test and negative cystoscopic findings and the latter was also excluded by negative signs of spinal cord lesions

Post micturition syncope which is well known is usually interpreted as orthostatic hypotension Valsalva maneuver and vasodepressor or cardioinhibitory reflex mechanism [3, 39] In Patient 3 the attacks of hypertension and tachycardia were triggered by micturition and by Valsalva maneuver but not by passive distention and contraction of the bladder

In normal subjects the initial decrease of blood pressure induced by micturition or Valsalva maneuver would be readily compensated by the reflex mechanism of buffer nerves and an overshoot phenomenon is often observed [1] If one has stenotic common carotid arteries the reduction of the carotid sinus pressure after voiding or Valsalva maneuver would be greater than the fall of systemic pressure Hypertensive attacks could not be attributed to the destruction of the carotid sinus baroreceptors because the patient s carotid sinus function was well preserved to external massage

Accordingly it may be supposed that the attacks of post micturition hypertension associated with tachycardia might have been the results of reinforced overshooting of carotid sinus

Table 1 Laboratory findings suggesting activity of inflammation

Items	Patient 1 (I T)	Patient 2 (K K)	Patient 3 (Y M)
Erythrocyte sedimentation rate	46 mm /hour	64 mm /hour	136 mm /hour
CRP test	+	–	+ + + +
RA test	–	–	–
ASLO	x166	x250	x500
Serum protein	8 2 Gm /dl	6 6 Gm /dl	8 0 Gm /dl
albumin	31%	50%	46%
α globulin	9%	1%	4%
α globulin	12%	11%	13%
β globulin	18%	11%	9%
γ globulin	30%	27%	28%
A/G	0 45	1 0	0 85

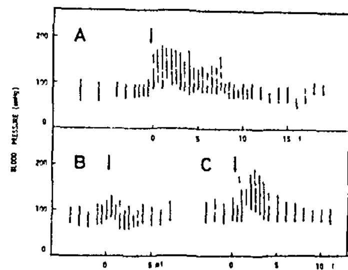


Fig 5 Blood pressure response after natural micturition (*A*) involuntary urination with an indwelling catheter (*B*) and voluntary urination after filling the bladder with water (*C*) *Apparent elevation of blood pressure was observed in A and C* but not in *B*

with prednisolone reliably controlled both the severity and the duration of hypertensive attacks after voiding Fig 5 *A* represents the response of blood pressure after natural micturition *examined on the thirty fifth day of steroid therapy* when hypertensive attacks associated with micturition had been reduced The elevation of blood pressure was most prominent immediately after micturition and lasted only *about eight minutes at this time Forty four days after the* beginning of steroid administration the attacks of post micturition hypertension completely disappeared and the elevation of blood pressure caused by Valsalva maneuver *subsided*

Discussion

Paroxysmal or transient hypertension is often observed under specific clinical conditions such as *psychic excitement* increase of intracranial pressure, *convulsion, disruption of the buffer nerves* spinal cord lesions pheochromocytoma, and administration of sympathomimetic or parasympatholytic agents and other vasoconstrictive materials Neurogenic hypertension especially that caused by the interruption of the buffer nerves including the baroreceptors [16 22] is interesting with regard to the recognition of the role of baroreceptors in regulating blood pressure Lampen[16] reported ten cases of transient hypertension *induced by polyneuritis affecting the buffer* nerves Kezdi[17] demonstrated that the blocking of the bilateral carotid sinus nerves with procaine produced prompt and marked elevation of blood pressure and heart rate Tuckman Slater and Mendlowitz[21] showed similar results after blocking sinus nerves The significance of the sinus nerves in the hypertension induced by carotid arterial occlusion is well known [20 21] It is also generally accepted that elimination of the buffer *nerves or occlusion of the common carotid* arteries result in hypertension and tachycardia by increased sympathetic cardiovascular activity [2 26 27] Normally the blood pressure and heart rate are well maintained at physiologic levels by the buffer nerves continuously responding to the fluctuating systemic blood pressure

In aortitis syndrome hypersensitivity of the carotid sinus nerves[4 5 7] upon external carotid sinus pressure is commonly seen as dizziness and fainting with hypotension and bradycardia Although hypertension in this disease seems to be a reversed form of hypotension both phenomena could be explained as the different expressions of *the dysfunction of the baroreceptors We believe* that the paroxysmal hypertension reported in

this paper might be a specific type of neurogenic hypertension

In Patient 1 pheochromocytoma and glomus tumor [3] were strongly suspected since a positive phentolamine test and a pulsatile neck tumor were noted These were excluded however by normal urinary catecholamines and evident effect of steroid hormone on the attacks Phentolamine yields effective adrenergic blockade and blocks not only the elevation of blood pressure in pheochromocytoma but also the pressor response elicited by stimulation of the sympathetic nerves and the pressor response induced by the occlusion of common carotid arteries [5] Hexamethonium which sufficiently suppressed the attacks in Patient 1 provides an effective blockade of the sympathetic ganglia

The clinical symptoms and the effect of steroid hormone in Patient 2 closely resembled those in Patient 1 Both patients had not only hypertension but also tachycardia during attacks Therefore we considered that the paroxysmal hypertension in these patients might have been derived from the sympathicotonic state induced by the dysfunction of the baroreceptors For instance if the systemic blood pressure was slightly reduced their stenotic carotid arteries would have caused severe reduction of the carotid sinus pressure with a subsequent sympathicotonic state Localized pressure on carotid arteries such as flexion of the neck could provoke the same effects Besides the stenotic lesions might have interfered with the carotid sinus pressure responding to the raised systemic blood pressure resulting from the sympathicotonic state and prolonged the duration of hypertension and tachycardia Slight inflammatory impairment of the baroreceptor itself and inflammatory infiltration which stiffened the arterial wall around the baroreceptors were also presumed to elicit the hypertension when the systemic blood pressure was elevated Because such lesions would reduce sensitivity of the baroreceptors hypertension was allowed to persist Sudden aggravation followed by rapid recovery of the inflammation of the baroreceptors or of the stenotic carotid arteries was also thought to be able to produce paroxysmal hypertension The effect of steroid hormones on the attacks might be interpreted as the result of relief of inflammatory lesions of the carotid arteries or of the baroreceptors

As a rule during an attack of angina pectoris the blood pressure and the pulse rate do not change remarkably [8] On the other hand hypertension and tachycardia are apparent precipitating factors of angina pectoris and the electronic carotid stimulator recently introduced for the treatment of severe uncontrolled angina pectoris[29,30] and diastolic hypertension[22,31] was reported to be very effective Therefore in our patients with aortic regurgitation the anginal pain and the electrocardiographic changes observed during attacks could be considered to be the result of hypertension and tachycardia Although the turnover rates of renin and angiotensin are relatively short [32,33] renovascular mechanism was considered unlikely to have produced the paroxysmal hypertension with tachycardia lasting for only a few hours

It is difficult to understand the mechanism of post micturition hypertension in Patient 3 Pheochromocytoma especially in the bladder [35] and autonomic hyperreflexia associated with spinal cord lesions[36,37] are also characterized by paroxysmal hypertension with voiding The former was ruled out by a negative histamine test and negative cystoscopic findings and the latter was also excluded by negative signs of spinal cord lesions

Post micturition syncope which is well known is usually interpreted as orthostatic hypotension Valsalva maneuver, and vasodepressor or cardioinhibitory reflex mechanism [3] In Patient 3 the attacks of hypertension and tachycardia were triggered by micturition and by Valsalva maneuver but not by passive distention and contraction of the bladder

In normal subjects the initial decrease of blood pressure induced by micturition or Valsalva maneuver would be readily compensated by the reflex mechanism of buffer nerves and an overshoot phenomenon is often observed [1] If one has stenotic common carotid arteries the reduction of the carotid sinus pressure after voiding or Valsalva maneuver would be greater than the fall of systemic pressure Hypertensive attacks could not be attributed to the destruction of the carotid sinus baroreceptors because the patient s carotid sinus function was well preserved to external massage

Accordingly it may be supposed that the attacks of post micturition hypertension associated with tachycardia might have been the results of reinforced overshooting of carotid sinus

Table I Laboratory findings suggesting activity of inflammation

Items	*Patient 1 (I T)*	*Patient 2 (K K)*	*Patient 3 (O M)*
Erythrocyte sedimentation rate	46 mm /hour	64 mm /hour	136 mm /hour
CRP test	+	−	+ + + +
RA test	−	−	−
ASLO	x166	x250	x500
Serum protein	8 2 Gm /dl	6 6 Gm /dl	8 0 Gm /dl
albumin	31%	50%	46%
α globulin	9%	1%	4%
α globulin	12%	11%	13%
β globulin	18%	11%	9%
γ globulin	30%	27%	28%
A/G	0 45	1 0	0 85

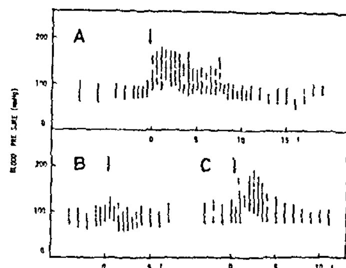


Fig 5 Blood pressure response after natural micturition (*A*) involuntary urination with an indwelling catheter (*B*) and voluntary urination after filling the bladder with water (C) Apparent elevation of blood pressure was observed in *A* and *C* but not in *B*

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Discussion

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In aortitis syndrome hypersensitivity of the *carotid sinus nerves*[4, 5, 22] upon external carotid sinus *pressure is commonly* seen as dizziness and fainting with hypotension and bradycardia Although hypertension in this disease seems to be a reversed form of hypotension, both phenomena could be explained as the different expressions of the dysfunction of the baroreceptors We believe that the *paroxysmal hypertension reported in*

this paper might be a specific type of [illegible] hypertension.

In Patient 1 pheochromocytoma and [illegible] tumor [1] were strongly suspected since a [illegible] phentolamine test and a pulsatile neck [illegible] were noted. These were excluded, however, [illegible] normal urinary catecholamines and evident effect of steroid hormone on the attacks. Phentolamine yields effective adrenergic blockade and blocks not only the elevation of blood pressure in pheochromocytoma but also the pressor response elicited by stimulation of the sympathetic nerves and the pressor response induced by the occlusion of common carotid arteries.[23] Hexamethonium which sufficiently suppressed the attacks in Patient 1 provides an effective blockade of the sympathetic ganglia.

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As a rule, during an attack of angina pectoris [illegible]

[illegible] tachycardia during [illegible]

It is difficult to understand the [illegible] of post-micturition hypertension [illegible] Patient 1. Pheochromocytoma, especially in the bladder,[illegible] and autonomic hyperreflexia [illegible] with spinal cord lesions[illegible] are also [illegible] paroxysmal hypertension with voiding. The former was ruled out by a negative [illegible] and negative cystoscopic findings, and the [illegible] was also excluded by negative signs of spinal cord lesions.

Post-micturition syncope, which is well known, is usually interpreted as [illegible] Valsalva maneuver and [illegible] reflex mechanism [illegible] the attacks of hypertension [illegible] triggered by micturition and by [illegible] but not by passive distention and [illegible] of the bladder.

[illegible]

[illegible]

Table I Laboratory findings suggesting activity of inflammation

Items	Patient 1 (I T)	Patient 2 (K K)	Patient 3 (T M)
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α_2 globulin	12%	11%	13%
β globulin	18%	11%	9%
γ globulin	30%	27%	28%
A/G	0 45	1 0	0 85

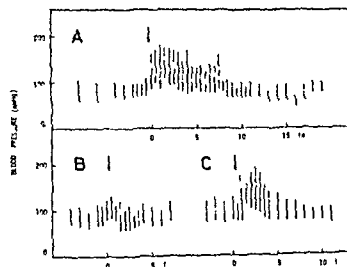


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reflex, and that the stenotic lesions might also have inhibited elevation of carotid sinus pressure, allowing the hypertension and tachycardia to persist

Morris and McIntosh[10] reported an interesting case of angina pectoris provoked by micturition They presumed that the anginal attacks might be attributed to the overflow of the nervous tone from the higher center through the vagus resulting in coronary artery constriction Like this reported case distension and contraction of the bladder did not produce any attacks in our patient This would suggest close correlation between the onset of hypertensive attacks and facilitation of micturition from the higher center, but its actual means were obscure

It is also interesting that the attacks were initiated by steroid therapy and finally ceased with its continuation We considered that the carotid sinus reflex might hardly have worked on the highly obstructed carotid arteries before treatment and that the attacks might have been observed only during the period when the stenotic lesions were slightly relieved The disappearance of the attacks would suggest complete recovery from the obstructive lesions

The actual mechanisms of paroxysmal hypertension observed in patients with active aortitis syndrome are not completely clear but our hypotheses would offer possible explanations of the attacks in these patients Thus these unique hypertensive episodes may be noteworthy from the viewpoint of the role of buffer nerves in blood pressure control

Summary

Three patients with aortitis syndrome exhibited paroxysmal hypertension which seemed to result from baroreceptor dysfunction All of the patients had signs of active inflammation of aortitis syndrome and stenotic carotid and subclavian arteries During the attacks the blood pressure rose to at least 230 mm Hg systolic and the heart rate exceeded 100 However, with prolonged administration of steroid hormones, the attacks ceased

In two patients with dilated thoracic aortas and aortic regurgitation the attacks of paroxysmal hypertension occurred without apparent precipitating factors and were followed by anginal pain with marked ST depression The sympathicotonic state resulting from the disturbance of the baroreceptors was considered to be responsible for the attacks In another patient, the attacks occurred in the course of treatment with a steroid hormone and were provoked only by voluntary micturition This post micturition hypertension was presumed to be an expression of abnormal overshooting following a fall in blood pressure after voiding

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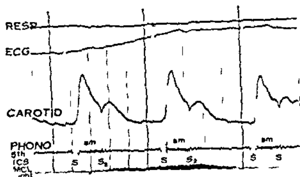


Fig 1 Phonocardiogram depicting the systolic murmur (SM) Time lines 0 04 second Abbreviations resp = re piration ECG = electrocardiogram ICS = intercostal space MCL = mid clavicular line S = first heart sound S = second heart sound

The lung scan was performed after injection of I macroaggregated albumin with an Ohio Nuclear dual 5 inch rectilinear scanner

Cardiac pressures were recorded on a multi channel Electronics for Medicine recorder with a Statham transducer

Discussion

A systolic flow murmur associated with embolus to the pulmonary artery was first reported 95 years ago by Litten[1] The present report is the first to our knowledge that records the disappearance of a pulmonary embolic flow murmur with improved pulmonary perfusion during anticoagulant therapy A variety of murmurs have been described in association with pulmonary emboli In some instances the diag nosis was established at autopsy ' ' Most murmurs are located at the second to fourth left intercostal space[2] are generally systolic in timing and are occasionally accompanied by a diastolic murmur in the same area' " Apical interscapular[2] left subscapular right subscapular ' and right infraclavicular mur murs have also been described Radiation has been noted in a variety of distributions which include the precordium ' the neck ' the left or right axilla and the right lower sternal bor der

The proposed mechanisms for these murmurs have included the protrusion of clot through the pulmonic valve partial obstruction of a major pulmonary artery which results in its relative stenosis ' and chronic pulmonary hypertension with resulting pulmonary valve insufficiency

Of great interest is the rare association of a

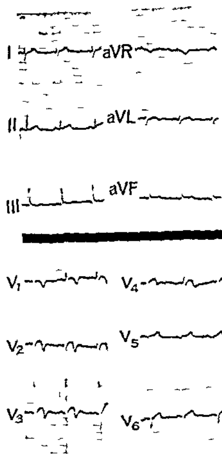


Fig 2 Electrocardiogram on admission See text for description

continuous murmur with pulmonary embolus Goodwin Harrison and Wilkin described a 29 year old patient with a six month history which was compatible with recurrent pulmonary em boli A continuous murmur was heard over the right upper chest and axilla Angiography and postmortem examination documented major bilateral pulmonary emboli The murmur was attributed to a continuous gradient across a partial embolic obstruction of a right upper lobe artery In a more completely studied case Claudio and co workers' described a 48 year old patient with a continuous musical murmur at the second left intercostal space which radiated to the right lower sternal border Cardiac catheteriza tion revealed a pressure gradient of the right lower lobe branch of the pulmonary artery The proximal pressure was 84/25 mm Hg and the distal pressure was 54/23 mm Hg. The patient was operated upon and thrombi were recovered from the right and left pulmonary arteries The

Flow murmur associated with partial occlusion of the right pulmonary artery

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Harvey Hecht, M D **
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Eugene Morkin M D ***
Boston Mass

A variety of abnormal auscultatory findings, including murmurs,[1-17] have been described in association with pulmonary emboli We have recently observed a youth with an acute embolus which partially occluded the right pulmonary artery An ejection murmur, maximally heard over the right chest, gradually disappeared in association with improved perfusion to the right lung This report draws attention to the fact that flow murmurs can occur in the setting of an acute embolus which partially obstructs a pulmonary artery and documents the disappearance of the murmur with dissolution of the embolus

Case report

An 18 year old white male student was admitted to Beth Israel Hospital because of a history of syncope three days prior to admission a subsequent complaint of shortness of breath with exertion and the finding of a new murmur

The patient was in good health until one week prior to admission when he accidentally traumatized his left thigh on the edge of a table Localized swelling was noted Three days prior to admission the patient blacked out without warning for several minutes Seizure activity was absent Because of persistent exertional dyspnea following the syncopal attack the patient sought medical assistance and was hospitalized

Physical examination revealed a well developed male in no acute distress The blood pressure was 114/62 mm Hg pulse rate 88 per minute respiratory rate 16 per minute and rectal temperature 99 6 F Examination of the head and neck was normal The neck veins were not distended The examination of the lungs was normal Cardiac examination revealed a point of maximal impulse in the fourth intercostal space at the mid clavicular line There were no thrills Auscultation revealed a normal first heart sound The second heart sound was physiologically split with an increased intensity of the pulmonic component A grade II/VI systolic ejection murmur was best heard at the fourth and fifth intercostal space in the right mid clavicular line with radiation over the right chest (Fig 1) The intensity of the murmur increased with inspiration The left thigh was slightly tender and was swollen There was no evidence of deep calf tenderness or femoral thrombophlebitis

The chest x ray was normal The electrocardiogram had normal sinus rhythm at 60 per minute the QRS axis was + 11 and there was an S I q III pattern S T elevations were present in aV_F V_1 through V and inverted T waves were present in V through V (Fig 2) Cardiac fluoroscopy demonstrated normal heart motion normal cardiac chamber size and absence of calcification A lung scan revealed poor perfusion of the right apex right base and left base (Fig 3) Cardiac catheterization revealed right heart pressures which follow pulmonary artery 37/18 mm Hg mean 26 mm Hg right ventricle 36/4 mm Hg and right atrium 5 mm Hg There was no evidence of tricuspid regurgitation Pulmonary angiography revealed a large embolus that partially occluded the right main pulmonary artery and its branches (Fig 4) Angiography failed to reveal evidence of thrombus in the inferior vena cava

Anticoagulation was instituted with heparin followed by sodium warfarin The hospital course was marked by gradual symptomatic and electrocardiographic improvement The murmur diminished in intensity A repeat lung scan on day 12 at the time of the disappearance of the murmur revealed normal perfusion of the right apex and markedly improved perfusion of the bases (Fig 3) The subsequent course was *uneventful and the patient was discharged on the eighteenth* hospital day

Methods

The phonocardiogram was recorded on a Cambridge multichannel physiologic recorder with the filter in the H position

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Summary

An 18-year old male student presented with a brief history of syncope followed by shortness of breath with exertion and the development of a murmur over the right chest The symptoms and murmurs were related to a pulmonary embolus which partially occluded the right pulmonary artery and its major branches The murmur gradually diminished and disappeared when right pulmonary perfusion had almost returned to normal as determined by lung scan The association of pulmonic flow murmurs and pulmonary emboli is reviewed

The authors thank Dr Peter Schneider for performing the lung scans and for the translation of Litten s article

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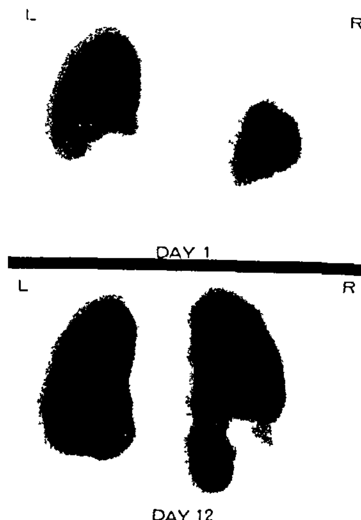


Fig 3 Lung scans Posterior views *Top* admission scan Absent perfusion of right apex right base and left base Bottom scan 12 days later Residual decrease in perfusion to the bases The murmur has disappeared

authors attributed the murmur to an embolic thrombus that mimicked a pulmonary branch stenosis The diastolic component of the continuous murmur was believed to be due to bronchial collateral circulation because of the absence of a significant diastolic gradient across the thrombus

Moser and co workers[6] were more successful in demonstrating a causal relationship between emboli and murmurs They described two patients with systolic murmurs located in one case at the third left intercostal space and in the other case below the left scapula Both murmurs extended beyond the second sound and increased in intensity with inspiration The first patient s murmur disappeared after embolectomy The second patient retained his murmur after embolectomy, but also had a persistent abnormality at



Fig 4 Pulmonary angiogram A large embolus partially occludes the right main pulmonary artery The clot extends to the upper and lower lobe vessels The arrows delineate the superior and inferior margins of the clot

the left base on lung scan It was concluded that pulmonary emboli can mimic the murmur of branch pulmonic stenosis by creating a turbulent blood flow at the point of partial obstruction

The branches of the pulmonary arteries can be partially occluded by pathologic processes other than congenital stenosis, thrombi or emboli Any process which partially occludes or constricts a major pulmonary artery branch can result in a flow murmur Examples include obstruction by echinococcus cysts [1] benign tumor of the pulmonary artery,[19] and chronic fibrous mediastinitis [21]

The patient herein reported presented with a murmur in an unusual location over the right anterior mid chest that is believed to be secondary to an acute embolic partial occlusion of the right main pulmonary artery and its major branches The murmur was characterized as grade II/VI, systolic in timing and maximal at the right mid chest The murmur gradually diminished and disappeared on the twelfth hospital day at a time when right pulmonary artery and capillary flow had almost normalized New or changing murmurs which occur in an obscure setting should arouse the suspicion of pulmonary embolus

reports of coronary disease in soldiers and young persons has focused on the occurrence of such changes among the young[11, 12]

The recent experimental observation by Burch Tsuie and Harb[3] that the virus Coxsackie B4 can damage cells in the coronary arteries and the development of the concept that exposure to viral infections in childhood can result years later in arteriosclerotic changes has provided additional emphasis to the importance of the early years of life This previously unrecognized possible relationship of viruses in the causation of heart disease provides an indication that similarly there may exist a large number of etiologic factors for each category of heart disease whose interrelationships have yet to be identified

Lloyd and Ciocco observed in the steelworker prospective study that while the pattern of white/nonwhite mortality ratios by age and cause of death were similar for steelworkers and the general populations the nonwhite deficit for arteriosclerotic heart disease (ASHD) was more marked for steelworkers Emphasis was directed at the importance of selective factors of employment the medical requirements of becoming employed and remaining employed and the physical capability of continued effort as the basis of better mortality experience of the employed population in contrast to the general population This observation of markedly lower age specific death rates for the employed population compared with the general population was previously demonstrated in an actuarial analysis by Myers

For approximately four decades there has been a continuous movement of the blacks from the rural south to the industrial centers of the north with subsequent exposure to the industrial environment and urbanization Actually 1 6 million blacks nearly one sixth of the total southern black population migrated north and west in search of job opportunities This constitutes a substantial population to explore various hypotheses

Our approach represents an initial step in this direction for cardiovascular disease the internal comparison of the mortality rates of Ohio black residents for those born in Ohio and those born elsewhere and the internal comparisons of a cohort of black steelworkers residents and migrants in the exploration of factors of selection in industrial employment

Methodology

The methodology and analysis are the same as in the previous migrant and steelworker studies[7, 8, 1, 17, 21]

The population examined in detail consists of Ohio residents born in Ohio and in Census designated regions of the United States Northeast North Central West South and outlying areas The figures for the State of Ohio are considered alone All deaths of Ohio residents who died in the United States and Canada (1960 1967) were included The causes of death used in this paper are the underlying causes as reported on death certificates and classified by the seventh revision of the International Statistical Classification of Diseases Injuries and Causes of Death

Regional population data by specific characteristics used as a basis for computing death rates are from the 1960 United States Census Ninety eight per cent of the Ohio nonwhite (ages 25 through 64) in the 1960 census population were Negroes The place of birth for the deceased was taken from information provided for the death certificate by relatives or other persons completing the certificate The regions of the United States used for the classification of place of birth were based on census groupings of the states Data on dates of migration were not available

Age groupings were based on the age of the person on the last birthday Average annual age specific death rates by color sex and nativity were computed on the basis of population data in the 1960 United States Census The population for the inter census years was estimated using a linear interpolation Death rates for the age span 45 through 64 years were age adjusted in 10 year groups by the direct method using as a basis the age distribution of the total population of the continental United States in 1960 The age group of 45 through 64 years was selected to provide a basis for comparison with earlier studies[2, 6]

The steelworkers data are from a cohort study of approximately 59 000 steelworkers employed in 1953 at seven steel plants in Allegheny County Pa Information obtained from plant personnel records included a complete work history from time of initial employment with the firm through 1966 birthdate birthplace race as well as identifying information needed for follow up Only 54 individuals (less than 0 1 per cent) were lost to follow up from 1953 1966 Copies of death certificates were obtained from appropriate state offices

Heart disease mortality among black migrants A study of Ohio residents (1960-1967)

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Why should the American Negroes from different geographic divisions experience large differences in mortality for hypertensive disease? Is the difference primarily a resultant of biologic differences between the two groups of United States Negroes in north and south, possibly caused by differential migration or, alternatively is it a resultant of differences in their socioeconomic and sociocultural environment? Is the hypothesis of differential migration that hypertension prone Negroes have remained in the South, whereas hypertension resistant Negroes have moved to the North, valid?"[1] Is industrial employment a selective factor in cardiovascular mortality among the migrants?

Considerable emphasis has been given to the desirability of studying these geographic differences, particularly for the Negro, as a means of developing some further insight in the etiologic factors associated with specific forms of cardiovascular disease[1]

These questions posed for coronary heart disease and cerebrovascular diseases as well are the basis for the present exploratory study Although extensive mortality data have accumulated relative to cardiovascular disease since Enterline and Sauer[2 4] identified and studied the magnitude and accuracy of geographic variation there have been comparatively few studies on migration within the United States

Sauer[5 6] conducted a series of studies on heart disease to ascertain whether the wide differences in death rates observed geographically could be due to migration patterns The studies, national in scope, were confined to whites It was shown that people born in states with high rates for coronary heart disease, continued to have high rates regardless of where they were living at the time of death Similarly, people born in states with low rates continued to have low rates after migration, although slightly higher than in states of origin Further, it was observed that 'out migrants' from the East South Central States to the Middle Atlantic States, had higher cardiovascular disease death rates than 'non migrants' from these states These observations indicate the possible influence of the early years of life on the subsequent development of coronary heart disease

Our interest in migration stems from observations derived from our previous studies in which migrants, particularly the nonwhite born in the South demonstrated an increase in risk in mortality for certain cancer sites[7 8] It was also shown in an analysis of steelworker coke oven employees where a high risk for lung cancer has been recognized that the excess of lung cancer was principally contributed by the black migrants from the South[9] Our present study constitutes an application of the same approach to cardiovascular diseases

Our hypothesis relates to the 'social and biological imprints" in the early years of life that combine with migration and subsequent environmental influences to bring about physiologic imbalances which supply the medium for the development of specific disease disability, and mortality risks[7 8]

Epstein[10] and others have emphasized the importance of studying the influences of early life on the later development of chronic disease The

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Table II Number of deaths and average annual death rates per 100 000 population for selected causes Ohio black females ages 45 64 age adjusted to 1960 United States population

Place of birth	All causes (001 999)	Coronary heart disease (420)	Endocarditis and myocardial degeneration (421-422)	Hypertensive cardiovascular diseases (440-447)	Cerebrovascular diseases (330 334)	Cardio vascular diseases (400-468)	Total diseases cardiovascular system (330 334) (400-468)
Ohio							
Rates	891.8	214 6	16 4	107 4	111 7	385 1	496.8
Numbers	1 09?	257	19	131	136	464	600
Northeast							
Rates	1 499 4	398 1	8 3	178 0	178 0	704 1	882 1
Numbers	151	39	1	18	18	70	88
North Central †							
Rates	1 000 9	242 7	17 7	119.5	118.5	435 7	554.2
Numbers	1,358	3?3	23	161	160	582	742
South							
Rates	1,854.5	377 1	30 1	233.2	237 4	743.3	980 7
Numbers	7,541	1,529	122	948	964	3 018	3,982
Total United States							
Rates	1,505.5	317 0	24 7	188 0	191.5	613.8	805.3
Numbers	9 127	1 897	147	1 132	1 150	3 684	4 834

West not included—n mbers too sm ll
†Incl des Ohi

rates for those born in the Northeast (2 319 5) with the highest rates for those born in the South (2 560 2)

The pattern of the overall rates for all causes shows substantial differences by region of birth It is evident that the findings by specific heart disease categories are not related to any selective diagnostic standards of heart disease and, there fore provide support to the consistency of the observed differences found in heart disease mortality among black males and females

Coronary heart disease (420) Table I shows that the United States born Ohio black males had an age adjusted rate (45 through 64) of 512 4 and when divided by region of birth showed lower rates for those born in Ohio (381 2) and higher rates for those born in the South (595 2)

Black females experienced similar relative changes in age adjusted rates (45 through 64) when the total United States born residents were divided by region of birth Those born in Ohio had the lowest age adjusted rate (214 6) and those born in the South the highest rate (377 1) compared with 317 0 for total United States rates

For both the males and females the excess rate for residents born in the South compared with those born in Ohio was consistently higher for each age group from age 35 on

In the sex comparisons (Tables I and II) the black males show a marked and consistent excess in mortality rates over the black females for each age specific group in all comparisons by total native born and by region of birth In the compar ison by birth in Ohio the male rate was three times that of the female in ages 35 through 44 and approximately one and a half to two times in the remaining age groups

Endocarditis and myocardial degeneration (421-422) In the region of birth comparison (Table I) the age adjusted rate for the black males born in the South showed 100 per cent excess compared with those born in Ohio (38 4 vs 16.8) This trend was consistent with the excess for coronary heart disease among black males in a similar comparison

Among the total black United States-born females (Table II) who had an age adjusted rate of 24 7 those born in the South had a higher rate (30 1) than those born in Ohio (16 4) which was similar to the pattern of excess for coronary heart disease (Numbers in the Northeast place of birth were too few for analysis among blacks)

Hypertensive cardiovascular diseases (400 447) The division by region of birth of the United States born black males who had an overall age adjusted rate at 191 9 shows that there was a markedly higher age adjusted rate for those born

Table I Number of deaths and average annual death rates per 100 000 population for selected causes Ohio black males, ages 45 64, age adjusted to 1960 United States population

Place of birth	All causes (001 999)	Coronary heart disease (420)	Endocarditis and myocardial degeneration (421 422)	Hypertensive cardiovascular diseases (440 447)	Cerebrovascular diseases (330 334)	Cardiovascular diseases (400 468)	Total diseases cardiovascular system (330 334) (400 468)
Ohio							
Rates	1 352 1	381 2	16 8	118 8	127 0	596 0	723 0
Numbers	1 415	403	18	129	134	635	769
Northeast							
Rates	2 319 5	698 1	18 9	144 2	169 2	974 0	1 143 2
Numbers	202	61	2	13	15	86	101
North Central †							
Rates	1 490 3	427 8	22 6	129 1	134 3	660 6	794 9
Numbers	1 787	508	27	158	159	791	950
South							
Rates	2 560 2	595 2	38 4	235 4	247 1	991 0	1 238 1
Numbers	10 136	2 356	152	932	978	3 923	4 901
Total United States							
Rates	2 115 0	512 4	32 4	191 9	202 6	838 9	1 041 5
Numbers	12 [illegible]3	2 9[illegible]6	187	1 111	1 169	4 845	6 014

West not included—numbers too small
†Includes Ohio

of vital statistics, and the underlying cause of death was coded by a trained nosologist according to the Seventh Revision of the International List

These analyses have focused upon the cumulative mortality 1953 1966, from cardiovascular diseases observed among black steelworkers who were born outside of Pennsylvania, in comparison with those born in Pennsylvania Unfortunately, the state of birth was not coded for the non Pennsylvania births, hence, it was not possible to examine the mortality for those born in specific sections of the country Review of original records however indicates that roughly 90 to 95 per cent of the individuals migrated to Pennsylvania from the Southeastern states

Seventy six per cent of the 7 277 black steelworkers in the study were born outside Pennsylvania Most of these men came from the Southeast many migrating to this area during and subsequent to the Second World War

The relative risks are based on use of Pennsylvania born black steelworker rates as a comparison They have been adjusted for age in 1953 and calendar years of follow up

An expected number of deaths was calculated for each age and calender year subgroup with the underlying assumption that the non Pennsylvania birth group and the comparison group have the same specific rate The total expected number of deaths is the sum of the specific rates for each subgroup, multiplied by the number of non Pennsylvania born workers at risk in the subgroup The relative risk is a weighted average of the observed and expected number of deaths in each subgroup, where the weights used are approximately proportional to the precision within each subgroup Because the relative risk is a weighted average it cannot be obtained directly by dividing the total observed deaths by the total expected deaths

A chi square test was used to test for significance of differences in risk between the non Pennsylvania born and the Pennsylvania comparison group of black steelworkers [22] In order to evaluate the findings further, results are also presented for certain selected work areas which had a sufficient number of black workers Work area classification is based on jobs held by the men in 1953

Findings

Ohio residents—migrant/nonmigrant

All causes (001 999) As shown in Table I, the age adjusted rate for United States born black males (ages 45 through 64) was 2 115 0 and when considered by region of birth, showed a lower rate for those born in Ohio (1 352 1), and much higher

and II the combined category emphasizes the differences observed There were marked differ ences in rates notably a decrease in the age adjusted rates for those born in Ohio and in contrast an exceptional excess for those born in the South compared with those born in Ohio Although the numbers are small the rates for those born in the Northeast were also markedly elevated

Total diseases cardiovascular system (300 334) (400-468) Among the black males and females (Tables I and II) the addition of the cerebrovas cular diseases emphasizes still further the relative differences by region of birth The substantial excess of the age adjusted rate for those born in the Northeast and still higher rate for those born in the South compared with those born in Ohio stands out

Steelworker migrant and nonmigrant Table III indicates that the black steelworkers who migrated experienced the same mortality overall from heart disease as did the Pennsylvania born steelworkers The observed and expected mortali ty for arteriosclerotic heart disease hypertensive heart disease and vascular lesions of the central nervous system for the selected work areas is also consistent with similar levels of risk in the industry regardless of birthplace

Although the relative risks of death from these causes differ somewhat among the work areas all differences are small enough to be attributable to random fluctuation

Discussion

Our study has taken the established geographic pattern of marked variation in resident mortality due to cardiovascular disease one step further and defined for one state by separation black Ohio born and migrant populations and grossly their degree of risk Further similar analyses of a large cohort of steelworkers contribute some interesting insights on the factors of selection in industrial employment

Ohio residents In the evaluation of the find ings we have been concerned with the extent that observed differences may be due to errors of the 1960 census In Siegel s recent comprehensive analysis preferred estimates were developed rela tive to both the 1960 and 1970 census (Table 5 Set D) The net per cent undercount for males for Negro and other races for ages 35 through 39 and each succeeding five year age group was 12 1 11 0 10 2 11 9 3 4 14 6 and overcount 0 2 in ages 65 through 69 For the nonwhite females for comparable ages the per cent of net undercount was 3 6 4 4 6 9 12 3 6 8 18 3 and 5 3

It is apparent that the consistent marked excesses of 60 to 100 per cent that we have observed in death rates of selected categories of cardiovascular disease for the black Ohio resi dents born in the South versus those born in Ohio could not be attributed to net undercount of the census in 1960

The relative pattern in our study of age specific death rates for males and females for the State is remarkably similar to that reported for the total United States[1] We have also considered the question of cause of death coding on death certif icates All causes of death were coded by the same nosologist in the same state for that period of years and it is extremely unlikely that the attending physicians throughout the state would be making their designation of the cause of death selectively by place of birth of the patient We have also considered age distribution and the age specific rates for ages 45 to 54 and 55 to 64 for black males and females which show the same patterns of differences

The fact that both the Ohio resident black males and females share this excess risk of a markedly elevated death rate for those born in the South compared with those born in Ohio for each of the major categories of cardiovascular disease indicates that at least some common factors are affecting both sexes to a certain level and some additional factors are affecting the males to account for the much higher rate over that of the females

The impression is that of a carry over among the blacks of a higher cardiovascular risk from the South among the migrants to Ohio Some support to this concept is indicated when the Ohio black male residents born in the South are further divided by region of the South The age adjusted rates (45 to 64) for black males born in the South Atlantic division were notably higher than the rates for those born in the South 612 5 for coronary 260 1 for hypertensive and 265 5 for cerebrovascular heart diseases The South Atlan tic division with the highest rate for the specific category of heart disease in our study coincides geographically with very high rates in the United States data

In a prior United States study it was found that for residents of the Middle Atlantic and East North Central divisions the nonwhite

Table III Comparison of cardiovascular mortality by selected work areas and birthplace for black steelworkers observed and expected deaths, 1953 1966, and relative risks* for heart disease

	Arterio sclerotic heart disease (420)	*Hypertensive heart disease (440 447)*	*Vascular lesions of the central nervous system (330 334)*	*Cardiovascular diseases (400 468)*
All work areas				
Number non Pennsylvania born	*5,558*			
Observed deaths	245	62	116	377
Expected deaths	243 0	62 8	109 8	377 1
Relative risk†	1 01	0 98	1 07	1 00
Selected work areas				
Coke plant				
Number non Pennsylvania born	*721*			
Observed deaths	31	5	15	43
Expected deaths	28 6	5 5	14 0	42 5
Relative risk†	1 20	0 82	1 17	1 03
Blast furnace				
Number non Pennsylvania born	*823*			
Observed deaths	24	4	10	40
Expected deaths	23 3	4 6	10 1	40 2
Relative risk†	1 01	0 85	0 98	1 00
Open hearth				
Number non Pennsylvania born	*1 404*			
Observed deaths	59	11	28	87
Expected deaths	58 1	10 1	25 8	85 0
Relative risk†	1 02	1 13	1 12	1 03
Foundry				
Number non Pennsylvania born	*196*			
Observed deaths	10	0	4	12
Expected deaths	11 3	–	3 8	13 4
Relative risk†	0 72	–	1 09	0 75
Billet bloom and slab mills				
Number non Pennsylvania born	*179*			
Observed deaths	8	3	7	13
Expected deaths	7 9	2 8	6 6	12 5
Relative risk†	1 02	1 12	1 10	1 06
Merchant mills				
Number non Pennsylvania born	*286*			
Observed deaths	18	4	5	26
Expected deaths	16 9	4 3	5 1	25 9
Relative risk†	1 10	0 90	0 99	1 01

Pennsylvania born steelworkers used as comparison group
†Significance of relative risk based on summary chi square with one degree of freedom

in the South (235 4) compared with those born in Ohio (118 8) (Table I)

For the black females there was a decrease in rate to 107 4 for those born in Ohio compared with an increase of 100 per cent among those born in the South (233 2) The principal contribution to the overall *resident* Ohio rate for both the males and females was from those born in the South

In the sex comparison (Tables I and II) the black males and females had approximately the same age adjusted rates by region of birth, with a slight increase for males born in Ohio (age adjusted rate 118 8 vs 107 4)

Cerebrovascular diseases (300 334) For the black males and females (Tables I and II) the same pattern as was observed with hypertensive cardiovascular diseases occurred there was a marked difference in the total native born rate when divided by region of birth with the Ohio born rate less, and a comparative 100 per cent increase in the rate for those born in the South

Cardiovascular diseases (400 468) For the black males and females as evident in Tables I

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Relative risk†	1.20	0 82	1 17	1 03
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Relative risk†	1 02	1 13	1 12	1 03
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Number non Pennsylvania born	*179*			
Observed deaths	8	3	7	13
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Cardiovascular diseases (400 468) For the black males and females as evident in Tables I

Table IV Coronary heart disease (420)

Place of birth	*White males*	*White females*
Ohio	600 6	153 8
Northeast	668 8	187 3
South	630 1	177 9
West	509 3	128 0

Basically for coronary heart disease (420) the white males and females show the highest rates for those born in the Northeast and the lowest rates for those born in the West Among the males the white have a much higher rate than the black for each region of birth except for the Northeast Among the females the black have a much higher rate than the white 214 6 vs 153 8 for those born in Ohio and 377 1 vs 177 9 for those born in the South

In terms of methodology our basic migration resource which is available in each of the states has been proved effective as a means of further refining the characteristics of study populations in the analysis of mortality risks for cardiovascular disease

The application of this approach to industrial prospective studies has further enabled a more accurate assessment of selective *factors which* influence mortality due to cardiovascular dis*ease*

It is hoped that other investigators conducting similar studies will be able in progressive steps to develop appropriate linkage data on migrants relative to endemic factors in the early years of life the patterns of migration and the subsequent sequence of social environmental and industrial influences

Summary and conclusions

In a demographic study the black Ohio residents were characterized by those born in Ohio and those born in other regions of the United States and comparisons were made of rates for all deaths (1960-1967) for coronary heart disease (420) endocarditis and myocardial degeneration (421-422) hypertensive cardiovascular diseases (440-447) cerebrovascular diseases (300 334) cardiovascular diseases (400 468) and total diseases of the cardiovascular system (300 334) (400 468)

The division of the total United States born Ohio residents by region of birth provided marked differences in the age adjusted rates in the relative comparisons.

The black males and females born in the South had a markedly higher age adjusted death rate (ages 45 to 64) than those born in Ohio in each of the categories of cardiovascular diseases studied

For coronary heart disease the age adjusted death rate for the black males showed a marked excess over the black females for each region of birth, whereas for hypertensive cardiovascular diseases the black males and females had similar age adjusted rates for each region of birth

The findings indicate a carry over among the black of a higher cardiovascular risk among those born in the South and lend support to the concept of the influence of the endemic factors in the early years of life

In the prospective study of black steelworkers it was observed that migrant and nonmigrant workers had approximately the same mortality for cardiovascular disease overall and when specific work areas were considered Selective factors of employment of medical screening and capability of continued employment in strenuous environments were considered the most likely basis for the similar mortality experience

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reported as life time migrants'* had nearly twice the rates for hypertensive heart disease than those reported born in these divisions The rates for the nonwhite 'life time migrants were intermediate between the high rates observed for residents of the South and low rates for those born in the northern divisions''

On the basis of our findings it may be postulated that in general, the blacks who migrated to Ohio were more susceptible to hypertensive heart diseases Further the susceptibility may be a *reflection of a complex of endemic factors* sustained in the early years of life Generally, in the South, most markedly among the black, the succeeding generations have been *exposed to a* socioeconomic climate of deprivation which has developed among some portion of the population, social and biologic imprints which constitute the physiologic imbalance, the acquired milieu for subsequent risk to environmental stresses and the development of specific diseases Conversely, following migration for some population subgroups an improvement in the standard of living as well as medical care may result in a reduction *of certain diseases*

The Ohio born black residents with the markedly lower rate for each of the categories of cardiovascular diseases in particular hypertensive *heart disease, would constitute first and* second generations of the migrants from the South It could be postulated that adaptation by these population groups over time, to whatever endemic socio environmental, and medical factors were involved in Ohio, provided a basis for *the marked decline in rate The basic observation* of change in mortality experience among migrants and descendants has been well established in inter country studies

The migrants from the South although sustaining an overall increased mortality risk for cardiovascular disease, nevertheless, most likely consist of population subgroups with a wide range of biologic attributes and capacities In turn, each of such population subgroups may be subjected *after migration,* to the same and different complexing factors which may adversely affect or improve their health risk to specific causes of death

Steelworker population The observation derived in this study of an equal risk in the coronary *heart disease among black* migrant steelworkers in comparison with Pennsylvania born steelworkers, was unexpected and poses a number of questions In contrast, as *previously mentioned* we had observed for another cause of death lung cancer among coke oven workers, that the excess of risk occurred primarily among the migrants from the South (33 of the 35 lung cancer cases were from the South)

In the evaluation of the findings on cardiovascular disease, one should consider that all specific work areas presented here involve basic production and thus selective factors were in operation *all workers would have to be physically fit* at time of employment in order to meet the job requirements This pre employment medical selection would tend to select out any individuals with obvious predisposing risk factors for cardiovascular disease The selective factors would further retain those workers with the capacity to consistently perform strenuous physical work Further, assuming that hypertensive heart disease would have a latent period if endemic fac*tors were involved in the early years of life then,* somehow, in the group employed either these factors were not present or, if present, they were mitigated by the combination of the selective employment *the nutritional requirements* of heavy industry, and the improved standard of living

We have no way of determining just what combination of circumstances was in operation that leads to an equal mortality risk for coronary and hypertensive heart disease among black *migrant and nonmigrant* steelworkers, other than the selective factors mentioned We recognize however, that a further comparative refinement of these employed populations in selected work areas, by duration of employment would be appropriate Environmental and health data during intervening years since migration are also highly desirable but are *not available*

Our findings should provide the basis for more questions and perhaps a redirection of some epidemiologic approaches in the eventual analysis of the combination of the early events of life and the subsequent events of migration

Migrant methodology In consideration of mortality *experience of black vs white populations by region of birth* Table IV *for coronary* heart disease age adjusted rate (45 to 64) is included for comparison

Native born residing in states other than state of birth at the time of census enumeration and a native born decedent whose residence at the same time of death is not *his state of birth* (page 168)

Fundamentals of clinical cardiology

The heart in myasthenia gravis

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In many disorders of muscle and connective tissue the disease phenomena referable to the cardiovascular system do not present as a gross part of the clinical picture during life and it is usually in a department of pathology—the "palace of truth —that cardiac involvement has been recognized We can apply this statement to patients with myasthenia gravis in whom abnormalities of cardiovascular function may appear minimal compared to the morbid anatomical changes that have been described Diverse authoritarian attitudes to the problem of heart disease in myasthenia gravis are illustrated by the following examples Rowland and associates discussing pathologic data have written that whatever the nature of these changes the frequency with which they are encountered suggests that the relationship is more than coincidental and that any theory of pathogenesis must take them into consideration Oosterhuis[2] maintained that the cardiac muscle does not participate in the myasthenic process according to our understanding of the pathophysiology The probable answer as is so often the case lies in selecting the appropriate variables before making generalizations for both the above statements are not incorrect

Morbid anatomy

The earliest evidence for morbid anatomical changes in myasthenia gravis goes back to 1901 when Weigert noted groups of abnormal cells in the myocardium and epicardium of a patient who had died with the diagnosis of thymoma and myasthenia He attributed the origin of these cells to secondary dissemination from the thymoma

According to Rottino Poppiti and Rao further study of the histopathology has since indicated that the thymic tumor in this case was nonmalignant and the inference must be that Weigert was describing lymphorrhages Buzzard[5] in 1905 described fairly numerous lymphorrhages (groups of lymphocytes) in left ventricular and skeletal muscle" and can thus claim credit for the first categoric description of a cardiac lesion in association with myasthenia gravis The comprehensive review by Rottino of the literature up to 1942 indicated that examples of microscopical lesions had also been described by Marie Boutier and Bertrand[6] Mella[7] and Barton and Branch[8] varying from scanty lymphocytic infiltration to frank diffuse myocarditis Rottino Poppiti and Rao described extensive changes in their case involving the entire thickness of the myocardium The microscopic pathology found was myofibrillar necrosis inflammatory changes with edema hemorrhage lymphocytic infiltration and large irregular histiocytes In later years Mendelow[9] Russell Rowland and associates[1] and Huvos and Pruzanski[1] all found similar micropathology but Russell emphasized the lack of specificity of the lesions since they can be seen in rheumatoid arthritis severe toxemias and certain endocrine conditions such as thyrotoxicosis and Addison s disease The importance of Russell s paper as far as the cardiovascular system is concerned is that she did describe the types of abnormalities that might be found in the myocardium using a classification similar to that used to describe striated muscle pathology

Fig 1 and 2 show an example of type I changes found in the left ventricle and indicate the striking inflammatory like lesions that have been described Such changes could be compatible with a myocarditis and do not appear specific

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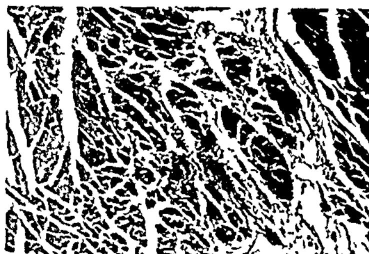


Fig 1 Left ventricle Several foci of mainly mononuclear cellular infiltrate in and around necrotic myocardial fibers (hematoxylin and eosin ×100)



Fig 2 Left ventricle Higher power view showing atrophic and necrotic muscle fibers with accumulation of mononuclear cells mainly lymphocytes (hematoxylin and eosin ×450)

Table I *Autopsy data indicating the pathologic* lesions found in the myocardium (Types I to III of Russell) and their association with thymoma

Reference No	Autopsies	Pathologic type 1	2	3	Normal
10	5	3 (2)	0	1	1
1	26	3 (?)	3	0	20
12	31	12 (9)	4	0	15
2	13	0	2	0	11
	75	18 (11)	9	1	47 (63%)

Numbers of associated thymomas appear in parentheses

A well established feature of the pathologic data is the significant association of thymoma with the more severe type I (Russell) changes found in the myocardium The largest series is that of Genkins and associates,[12] who noted this association in a number of their 31 autopsies They found that Type I changes were present in nine instances out of 10 with thymoma and three instances out of 21 with no thymoma Such changes consisted of coagulation necrosis and inflammatory focal exudation, and were most marked in those patients where the myasthenia was associated with malignant thymoma Other authors have noted this important relationship [1,10,13] Table I summarizes the pathologic changes and their association with thymoma in the larger autopsy series available from the literature

Burke Medline, and Katz[14] reported a patient with giant cell myocarditis and myositis associated with thymoma and myasthenia gravis They observed that giant cell myocarditis is very rare and that a third of the 30 cases reported in the literature were associated with thymoma, with some of these patients having clinical myasthenia gravis It appears that this is yet another type of myocardial pathology that can be found associated with myasthenia gravis This association has been reinforced by others [15,16] Namba observed that five of seven patients with associated polymyositis and myasthenia gravis had giant cell myocarditis

It is important to consider the following factors in an evaluation of cardiac pathology in myasthenia gravis (1) Many patients with myasthenia are in an age group where coronary vascular disease might be expected to occur and give rise to pathologic changes in the myocardium This applies especially to men, where the peak incidence of myasthenia is in the sixth and seventh decade [17] The lack of specificity of certain of the minor myocardial changes in myasthenia gravis would indicate that this is an important consideration Furthermore the patients with associated thymoma appear to be in an older age group than those without [18] As Genkins has pointed out however arteriosclerotic changes should be easily differentiated from the more severe pathologic characteristics found in myasthenia gravis (2) The effect of irradiation to the thymus has to be considered in terms of potential inflammatory changes that could take place in both the pericardium and the myocardium under these circumstances Certain authors have described changes

which are not grossly dissimilar following irradiation of this general area [8,20] (3) Invasion of the myocardium and pericardium by a malignant thymoma is a possibility and we have seen "seeding" of the epicardial surface by such a tumor In general extension of the tumor appears to be more local than metastatic and may give rise to obstructive vascular changes especially when large vessels venous or arterial are involved (4) The apparent less than fortuitous coincidence in myasthenic patients of thyrotoxicosis rheumatoid arthritis certain anemias and other conditions that can affect the heart could also give rise to a pathologic process (5) The hypoxia hypercapnia acidosis and associated respiratory infection which may occur in the myasthenic crisis could give rise to alterations in heart muscle Bronchopneumonia is a common autopsy finding in patients with myasthenia gravis This disorder in itself may give rise to cardiac changes, and in one series where the association was pursued 39 per cent of 67 patients revealed inflammatory changes sufficient to warrant the term myocarditis [21]

Alterations of intracellular and extracellular potassium levels are likely to occur in myasthenia gravis and if hypokalemia was present this abnormality is stated to have a specific associated myocardial lesion [22] (6) The question of autoantibody formation associated with an excess of thymic tissue must be considered It is characteristic of autoimmune disease that the heart should be affected and there is no reason why on a similar basis to skeletal muscle antibody formation to cardiac muscle should not occur Serologic studies of patients with myasthenia gravis by Beutner Witebsky and Djanian[2] have demonstrated antibodies to both skeletal and heart muscle They described an antibody type SH occurring in 20 of the 80 patients that they studied serologically This has been further elaborated by Cossio and associates[3] who by means of immunofluorescent techniques found SH antibodies in the sera of 14 of 25 patients with myasthenia gravis Stewart and Snell[23] have described thymomas and thymic hyperplasia in a rodent *Praomys (Mastomys) natalensis* with concomitant myositis myocarditis and sialodacryoadenitis They thought that this combination suggested an autoimmune disease There is no doubt that this area requires further investigation as it may well be possible that myocarditis or the other major pathologic changes found in the myocardium bear no specific relationship to the myasthenic process but are a direct result of autoantibody formation

Pathophysiology

Involvement of the function if not the structure of cardiac muscle might reasonably be expected in patients with myasthenia gravis by simplistic extrapolation of the assumed mechanism of the disease Although there are no myoneural plates at the termination of cardiac innervation it is known that the autonomic nervous system may be involved in myasthenia The justifiability of such an assumption does not necessarily follow and this section deals with existing evidence albeit scanty of functional cardiovascular involvement in myasthenia gravis

Very few studies have been done in this area Kornfeld and Osserman[24] investigated 30 patients with *myasthenia gravis* none of whom had thymic enlargement evaluating the effect of carotid sinus pressure Tensilon Tensilon and carotid sinus pressure and atropine A series of 30 control subjects were also studied in a similar fashion but *no statistically* significant difference could be found between the cardiovascular responses of those patients with myasthenia and those without Since these patients were selected because they did *not have* overt evidence of cardiovascular disease and no thymic enlargement this creates a problem in determining the significance of a study when applied to all patients with myasthenia gravis Taquini Cooke and Schwab[27] studied the effect of vagal stimulation by carotid sinus pressure and mecholyl on patients with myasthenia gravis They could find no difference from what might be expected from normal controls The same applied to atropine Kuzin and Drelzinia[2] evaluated alterations in pulse rate arterial blood pressure and heart sounds in patients before and after thymectomy for myasthenia Improvements in these parameters were noticed such as conversion of sinus arrhythmia to normal rhythm They also stated that they noted an improvement in the functional state of the myocardium as measured by electromechanical phenomena specifically the dynamics of the electrocardiogram (ECG) Kohn Tucker and Kozokoff[28] have documented the beneficial effect of neostigmine on the ECG of a 26-year old white woman but it is very difficult

Table II ECG changes in patients with myasthenia gravis

Reference No	Patients	Conduction disturbances	ST T changes	Arrhythmias	Normal
27	14	0	0	0	14
31	12	0	6	0	6
28	31	8	23	0	3
29	26	1	22	1	3
37	24	11	15	1	10
33	97	20	13	3	62
34	41	3	13	6	21
Total	245	43	92	11	119 (49%)

to evaluate such ECG changes since so many factors may be involved *It was also considered* that she had an abnormal Master's test but the changes are unequivocally minimal

Clinical findings

The range of clinical findings in patients with myasthenia gravis can be protean Many patients are totally asymptomatic from the cardiac point of view but a few have the most striking clinical course which makes it very difficult to establish a common denominator A patient described by *Voog, Denis and Cabanel*[1] *had gross evidence of* severe cardiac failure which could possibly be ascribed to *involvement of the myocardium by a* myasthenic process On the other hand, it could have been due to incidental disease without any association with myasthenia

1 Symptoms and signs Generally there has been little in the way of specific symptoms for myasthenia gravis as far as the heart is concerned although *vasomotor instability is often men* tioned Taquini *Cooke and Schwab*[27] *have described patients who had palpitation, dyspnea* and mild hypertension It was not considered that any of these phenomena were specifically related to the myasthenia gravis Kohn Tucker and Kozokoff[29] and Ask Upmark[31] noted precordial oppression chest pain, tachycardia, and dyspnea Kuzin and Drelzinia stated that virtually all their patients had palpitation Goni[12] believed that one of his patients was suffering from excess vagal tone in view of her response to carotid sinus pressure but did not consider this to be specifically related to myasthenia gravis although autonomic phenomena have been described It is clear, however, that symptoms related to cardiac failure could have been associated with a signifi cant type of myocarditis *in myasthenic patients with thymoma* but that the myocarditis was an incidental finding at autopsy[11]

In addition concomitant diseases will give rise to their own appropriate symptoms In our own series there were no specific physical findings associated with myasthenia gravis which could not be explained by anxiety or coronary heart disease

2 Electrocardiogram There are many studies of the ECG in myasthenia gravis The findings vary from no abnormality at all in 14 patients studied by Taquini, Cooke and Schwab[2] *to* abnormalities in virtually every tracing in the *series of* Kohn, Tucker, and Kozokoff A combined series (Table II) indicates that at least half of the patients had abnormalities These consisted of conduction defects ST and T wave changes and arrhythmias

The largest series is that of Luomanmaki Hokkanen and Heikkila[33] Their data may be summarized as follows The ECG findings *are derived from a retrospective study* of 97 patients *A normal ECG was found* in 64 per cent and 11 per cent had abnormal ECG s consistent with their independent heart disease Nine per cent had minor ECG changes which were indistin guishable from their incidence in the normal population Fifteen per cent showed a terminal notching of the QRS complex (Fig 3)

It was concluded that no ECG evidence charac teristic of myocardial involvement exists in a majority of patients with myasthenia gravis It is possible but unlikely that the terminal changes in the QRS complex are significant as a sign reflecting myocardial pathology, nevertheless they can be found in normal healthy people This summation of a major paper reflects the opinion

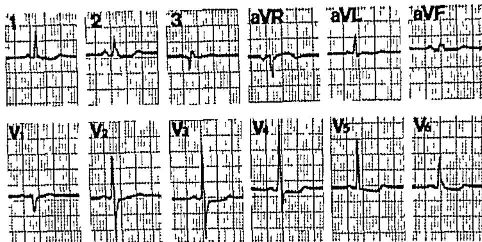


Fig 3 Illustration of terminal conduction defect in a male patient (R K age 48) Leads I II aV_R and V show this clearly

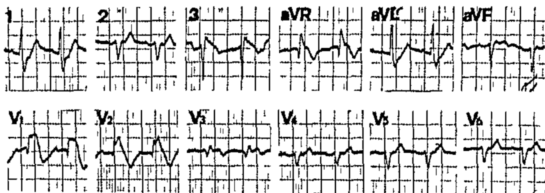


Fig 4 Illustration of right bundle branch block and left anterior hemiblock in a female patient (F B age 79) with myasthenia gravis and coronary heart disease

of the present author in reviewing his own patient data[3]

Interpretation of such data is generally very difficult in view of the minor changes found since many of the changes can be attributed to pre existing cardiovascular disease and are clearly not specific for myasthenia gravis In the author's series, out of 20 patients below the age of 60 years only five had ECG changes In those patients who were 60 or over 15 out of 21 had changes which could be compatible with coronary heart disease and would generally have been interpreted as such Our data are not like those of Kohn Tucker and Kozokoff[7] where 15 out of 18 of their younger age group had abnormalities In some of the autopsy cases where significant myocarditis had been found there were ST and T wave segment changes which would be compatible with the pathologic findings In others no ECG findings were present in the face of quite extensive myocarditis[13] Other myopathic conditions appear to give rise to more specific abnormalities and this is exemplified by ECG's simulating myocardial infarction and parietal block which are relatively common in patients with myotonia atrophica[15] Only one case of myasthenia was found which could be compared to such findings[26] that of a 25 year old white man who during a severe myasthenic crisis showed a tracing that was typical of extensive anterior wall infarction with the pattern of parietal block being manifested by abnormal left axis deviation Later these changes disappeared When this patient died necropsy revealed patchy areas of interstitial fibrosis scattered throughout the myocardium with no evidence of coronary artery abnormality

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Prognosis

Specific cardiovascular complications of myasthenia gravis have been very difficult to find except in isolated cases where associated myocarditis was a cause of death. The question of sudden death has been considered in many patients but documentation of a cardiovascular origin is always a problem since continuous ECG monitoring is the exception. In the series of Rowland and associates 13 of the 39 deaths described were sudden and unexpected. It is probable that one patient had extensive myocarditis but it is not certain as to the remainder. Because of an assumed increased vagal tone in such patients deaths have been attributed to fatal arrhythmias of the type associated with this situation. The more usual mode of death seems to be related to respiratory failure and any cardiovascular involvement could be functional in origin rather than due to a specific organic lesion secondary to myasthenia. It is relatively easy to assume arrhythmogenic electrical inhomogeneity of myocardial fibers in such patients because of associated electrolyte and blood gas abnormalities. In addition aggravation of pre existing cardiovascular disease could well occur.

Summary

The cardiac changes associated with myasthenia gravis have been reviewed and specific areas explored. There is no doubt concerning the involvement of the myocardium in this disease as indicated by clinical ECG vectorcardiographic and autopsy data. The doubt lies in the precipitating factor for the pathology found. On the one hand the whole picture could be a direct result of the pathologic process of myasthenia gravis. On the other hand the patient with myasthenia gravis during the natural history of the disease encounters many iatrogenic and coincidental variables which could influence the nature of the clinical findings and autopsy data. One fact seems reasonably clear. The association of myocardial pathology with thymoma especially malignant thymoma is well established for the more severe form of the myocardial disease. Furthermore the hypothesis that cardiac muscle antibodies give rise to such reactions is attractive although not fully resolved.

If such cases are excluded then there remain others where cardiac pathology could be due to other disease primarily coronary heart disease in the older age group. In addition the mode of death of some patients indicates that intercurrent respiratory problems could play a part. Most patients in this group do not seem to have cardiac abnormalities due to the pathologic process of myasthenia. There is in addition a small group where very striking cardiovascular findings suggestive of myocarditis are found. There is not necessarily a thymoma and no other specific etiologic factors can be found. These are rare cases and might still be related to disorders of immune mechanisms.

In conclusion it can be stated that although there is now a considerable body of evidence concerning the heart in myasthenia gravis the implication of specific pathology for this neuromuscular disorder affecting the heart must be considered in the traditional Scottish legal sense as not proven.

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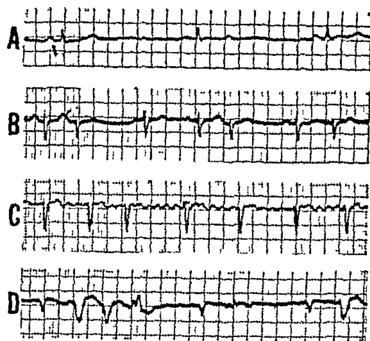


Fig 5 Illustration of arrhythmias that may occur in myasthenia gravis *A* Sinus bradycardia (R B female age 44) *B* Atrial premature beats (E S male age 63) *C* Atrial fibrillation (G N female age 63) *D* Atrial fibrillation with multifocal ectopic beats probably ventricular (H R female age 76)

Conduction disturbances appear to be quite rare other than the previously described terminal notching of QRS Bundle branch block is most unusual (Fig 4) but first degree A V block has been described [29]

Arrhythmias are equally unusual but were found by us in six (15 per cent) of the 41 patients with myasthenia gravis who had an ECG These consisted of sinus bradycardia, atrial and ventricular premature beats, and atrial fibrillation (Fig 5) With the exception of the patient with sinus bradycardia these arrhythmias occurred in the older age group and the findings could quite reasonably be attributed to coronary heart disease

3 Vectorcardiogram Alteration in vectorcardiographic loops prior to and after anticholinesterase treatment have been described by Ioffe, Anokhin, and Komarov [36] The abnormalities were slight and did not contribute significantly to the pathophysiology of the disease Moffa and associates[37] also took vectorcardiograms in 24 patients with myasthenia They were able to find areas of electrical inactivity in the QRS loop initial and particularly terminal loop disturbances in ventricular conduction, and left ventricular hypertrophy They observed that, generally, there was little difference between the findings in the younger and the older age groups but there are too few older patients in his series (five aged more than 50) to make this significant

4 Roentgenography There are no specific cardiovascular x ray features of myasthenia other than in association with other disorders or complications All our patients had either normal chest x rays or abnormal findings which could be attributed to coincidental disease Batt[38] conducted roentgenkymographic studies of the heart in myasthenia gravis He could find no characteristic findings and considered that previous abnormalities have been related to the use of prostigmine in such patients and associated with slowing of the cardiac rate

Cardiovascular therapy

The therapy of cardiac disorders in patients with myasthenia gravis requires some amendment since there are certain drugs which have to be given carefully, or not at all Weisman[39] noted that the use of quinidine in a patient with a supraventricular arrhythmia appeared to aggravate the myasthenia for which the patient was also under treatment In view of the well known neuromuscular effect of quinine this might be expected [40] Drachman and Skom[41] noted a striking increase in weakness in a 78 year old man who was being treated with procaine for premature ventricular contractions They believed that the procaine interfered with neuromuscular transmissions and that it was not indicated under these circumstances They felt that if arrhythmias of importance occurred in patients with myasthenia gravis other drugs combined with or preceded by cardioversion with the administration of potassium would be preferable Lidocaine may be another drug that has to be used cautiously The question of the effect of Dilantin on the neuromuscular synapse also gives rise to the possibility that it may be contraindicated in arrhythmias, but this is so far theoretical [42]

It has also been stated that morphine, which might be given for chest pain or in left ventricular failure, is potentially dangerous since vagotonic drugs may have an increased effect in patients with myasthenia It is known that morphine methadone and meperidine are potentiated by neostigmine,[43] so that if the patient is on neostigmine he may require less of these anodynes It should also be noted that anticholinesterinase medication may lead to profound bradycardia in certain cases

Electrophysiology and pharmacology of cardiac arrhythmias VIII Cardiac effects of diphenylhydantoin B

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III Cellular electrophysiological effects of DPH and possible mechanisms for its antiarrhythmic actions

The therapeutic actions of DPH probably are due to its effects on conduction refractoriness and automaticity of cardiac fibers Such effects may be mediated both by direct actions of the drug on the heart and by effects exerted through the cardiac autonomic nerves

Effects of DPH on conduction of the cardiac impulse effects on resting membrane potential action potential amplitude phase 0 upstroke velocity (V_m) DPH may exert several different actions on resting membrane potential action potential amplitude and phase 0 upstroke velocity (V_m) of both atrial and Purkinje fibers These actions seem to depend on (1) the concentration of DPH (2) the [K] in the extracellular environment and (3) the electrophysiological condition of the fibers that is whether resting membrane potential action potential amplitude and phase 0 upstroke velocity are abnormally low or within normal limits The extracellular [K] has pronounced influences on the electrophysiologic actions of DPH When [K] is low (<3 mM) low concentrations of DPH (1 to 3 μg/ml) may increase the resting membrane potential V_m of phase 0 and action potential amplitude of both atrial [5] and Purkinje fibers [52, 53] The membrane responsiveness curve also may be shifted to the left and upward indicating an increase in V_m at all levels of membrane potential at which an action potential can be elicited Conduction velocity also may be increased by DPH All these effects are particularly pronounced if these parameters initially are reduced as by exposure to cold mechanical trauma or toxic concentrations of digitalis (Fig 6) When resting membrane potential V_m of phase 0 and action potential amplitude are normal a low concentration of DPH does not have any effect When [K] is low higher concentrations of DPH (5 to 20 μg/ml) do not significantly alter the resting membrane potential V_m of phase 0 action potential amplitude or the membrane responsiveness curve and therefore do not influence conduction of the action potential

When the [K] concentration of the superfusate is at normal plasma values (4 to 5 mM) or slightly elevated DPH has more of a depressant effect on the action potential of both atrial and Purkinje fibers Low concentrations (1 to 3 μg/ml) do not increase the resting potential V_m of phase 0 or action potential amplitude as greatly as in low [K] although some improvement may still occur [6] Higher concentrations of DPH (5 to 20 μg/ml) depress these parameters and also may slow conduction The membrane responsiveness curve of Purkinje fibers is also shifted to the right indicating a depression of V_m of phase 0 at all levels of membrane potential at which an action potential can be elicited [54] This depressant effect is not as great as that of quinidine or procaine amide

The action of low concentrations of DPH (1 to 3 μg/ml) to improve resting membrane potential

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rectional conduction block consequent to these changes by any of the mechanisms we have described previously (see Figs. 2 *A* and *B* and Fig 3 of ref 56) Improvement of resting membrane potential or V_m by DPH might abolish the unidirectional block restoring a normal activation sequence in the reentrant pathway or speed conduction of the impulse in the reentrant pathway to such an extent that it would return to its point of origin before the cardiac fibers at this locus had recovered excitability (Fig 6) Therefore the reentering impulse would block before it could conduct back into the ventricles and premature beats due to reentry would be abolished Such an effect of DPH on reentry is strictly hypothetical and has not been demonstrated directly The effect of DPH on conduction of slow responses resulting from toxic concentrations of digitalis has not been investigated Since these actions of DPH to improve conduction may not occur when [K] is normal or elevated under these conditions antiarrhythmic effects may not be exerted by this mechanism Although DPH does slightly depress conduction in Purkinje fibers when [K] is in the normal range this effect is not as great as the action of quinidine or procaine amide which can block conduction in reentrant pathways Therefore it is uncertain whether DPH can exert any antiarrhythmic effects on reentry by the same mechanism as quinidine and procaine amide On the other hand we do not know the effects of DPH on diseased cardiac fibers with low membrane potentials or on cardiac fibers with slow response action potentials Selective drug depression of such cardiac fibers without significant depression of normal fibers remains a possibility Antiarrhythmic actions of DPH at normal plasma [K] may be exerted by other effects rather than on conduction of the primary impulse such as effects on delayed afterdepolarizations which may cause digitalis arrhythmias[35] effects on conduction of premature impulses or effects on spontaneous diastolic depolarization (see below)

Effects on action potential duration refractoriness and conduction of premature impulses The initiation of reentry and sustained reentrant arrhythmias may result from slow conduction and unidirectional block of premature impulses (Fig 7)[36] Antiarrhythmic drugs may exert therapeutic effects by modifying conduction of premature impulses

In both atrial and Purkinje fibers, when the membrane responsiveness curve is shifted to the left (low DPH concentration and low [K]) the effect of the drug is to speed conduction of premature impulses This action might abolish slowed conduction and unidirectional block of premature impulses which result in reentry although this has not yet been demonstrated

DPH also may improve conduction of premature impulses in Purkinje fibers even when the membrane response curve is not shifted by significantly shortening the action potential duration an action similar to that of lidocaine The effective refractory period is also decreased although the reduction is not as great as the reduction in action potential duration (Fig 7)[32] When this occurs the earliest premature impulses which can be initiated during repolarization arise from higher membrane potentials and therefore have a greater V_m and amplitude than do the earliest premature impulses initiated prior to drug administration As a result premature impulses should conduct more rapidly after DPH and both reentry due to slow conduction and unidirectional block of premature impulses would be abolished[5] (Fig 7) This effect occurs independently of [K] in the range of 3 to 5 mM and at a wide range of DPH concentrations (3 to 20 μg/mL) Shortening of the action potential duration and effective refractory period of Purkinje fibers might also have an antiarrhythmic effect by another mechanism We have previously described mechanisms whereby reentry might result from inhomogenous conduction of premature impulses through regions where Purkinje fiber action potential durations and effective refractory periods have been altered (see Fig 8 and 9 in ref 57) Our discussion of the possible antiarrhythmic actions of lidocaine in these situations may also apply to DPH (see Figs 6 and 7 in ref 58) Again experimental data demonstrating the ability of DPH to abolish reentry by shortening action potential duration have not been published

DPH does not change the action potential duration and effective refractory period of atrial fibers as much as in ventricular fibers Rather atrial fibers show minimal changes in these parameters after DPH administration This lack of a prominent effect on the effective refractory period of atrial fibers may be a cause of the ineffectiveness of DPH against most atrial arrhythmias Quinidine has a much greater effi

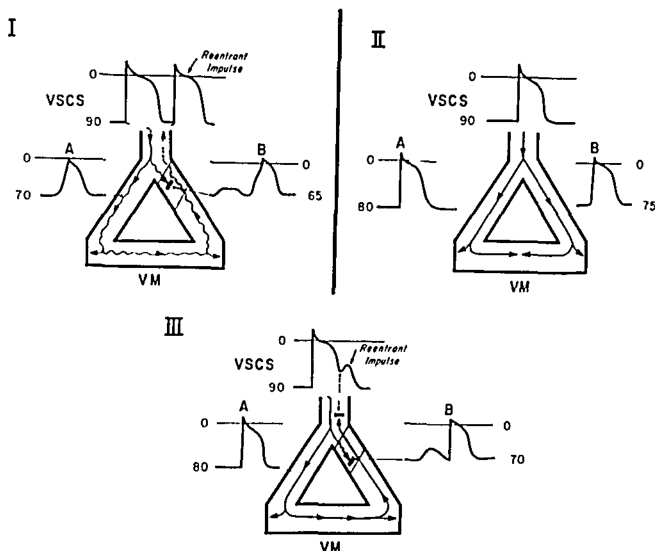


Fig 6 Possible mechanisms by which DPH may abolish reentry due to slow conduction and unidirectional conduction block when extracellular [K] is low *Panel I* shows reentry in a loop composed of Purkinje fiber bundles (*A* and *B*) and ventricular muscle (*VM*) by the mechanism which we described in *Fig 2 ref 56* Action potentials recorded from branch *A* arise from low membrane potentials and have a slow rate of depolarization resulting in slowed conduction through this branch as indicated by the wavy line and arrows The Purkinje fibers near the origin of branch *B (shaded area)* have still lower membrane potentials and there is unidirectional conduction block in this region there is only a low amplitude response during antegrade conduction block *(1st response under B)* and an action potential with a slow upstroke during retrograde conduction of the reentering impulse *(2nd response under B)* The impulse which is conducting retrograde in *B* enters the conducting system (VSCS) as the reentrant impulse In *Panel II* after exposure to a low concentration of DPH the membrane potential of the fibers in both branches *A* and *B* are more negative and the action potentials have more rapid upstroke velocities As a result conduction through branch *A* is more rapid and there is no longer antegrade conduction block in branch *B* reentry is absent and normal activation of the Purkinje fiber loop occurs *Panel III* shows how reentry might be abolished even if unidirectional block in branch *B* persists Again DPH causes membrane potential of the depressed fibers in the loop to become more negative Upstroke velocity of fibers in branch *A* increases and antegrade conduction speeds Even though membrane potential is more negative in *B* after DPH antegrade conduction may still block However conduction around the loop is now rapid and the impulse returns to the VSCS before fibers in this region recover excitability and conduction block of the reentering impulse occurs (see action potentials in VSCS)

V_m and action potential amplitude of both atrial and Purkinje fibers in vitro, when these parameters are low and when [K] in the extracellular environment is low[49, 52] may be responsible for some antiarrhythmic effects Digitalis toxicity often occurs in patients with a low plasma [K] [12]

Toxic concentrations of digitalis may cause a decline in membrane potential V_m and action potential amplitude of both atrial and Purkinje fibers[15] and may even convert the action potential to a slow response Reentry might occur due to combined effects of slowed conduction and unidi

back into the cell.[60] Such inhibition would result in an increase in intracellular [Na] and a decline in intracellular [K] An increase in intracellular [Na] might result in a decrease in the electro chemical gradient for Na and therefore V_m and action potential amplitude would decline A decrease in [K] would result in a decline in resting membrane potential and this would partially or completely inactivate the fast inward Na current These effects may result in conduction disturbances reentry or abnormal automaticity

The loss of myocardial K during digitalis toxicity is reflected by a marked increase in coronary sinus venous [K][61] Helfant and associates[62] have reported that DPH reverses this loss of K from the heart at the time it is abolishing the digitalis induced arrhythmias [2] DPH prevention of K loss and Na accumulation by guinea pig myocardial cells after digitalis intoxication also has been reported [63] Such effects may result from antagonism by DPH of the digitalis induced inhibition of the Na -K pump and restoration of more Na -K exchange and gradients The resultant decrease in [Na] and increase in [K] would restore resting membrane potential to normal increasing the availability of the Na carrier system Unfortunately other studies have failed to demonstrate any ability of DPH to prevent K efflux during digitalis intoxication and this question must be clarified [6, 67] If DPH can stimulate Na -K exchange pumping this effect might also explain the action of DPH to retard the decline of maximum diastolic potential in Purkinje fibers exposed to hypoxia Hypoxia depresses Na -K pumping and causes an increase in [Na] and a decrease in [K] [68]

In addition to possible effects on active ion transport DPH might affect membrane ionic conductances although as yet there are no studies to demonstrate this A possible increase in Na conductance has been postulated to mediate the increase in V_m seen in depressed cardiac fibers after exposure to DPH [5] and an increase in K conductance has been suggested to mediate its depressant effect on spontaneous diastolic depolarization and the acceleration of repolarization in Purkinje fibers [6] As we have mentioned above DPH can decrease V_m under certain conditions and this effect could result from a depressant effect of the drug on Na conductance and the fast inward current [7] The depressant effect of DPH on V_m of atrial fibers can be reversed by increasing [Na] in the perfusate suggesting that this depressant effect is due to a drug induced decline in Na conductance [5]

IV Effects of DPH on the nervous system as a mechanism for its antiarrhythmic actions

Cardiac arrhythmias associated with pathological conditions such as myocardial infarction as well as digitalis induced arrhythmias may result in part from altered nervous system activity [1, 72] and the effects of the nervous system on electrophysiological events in the heart After myocardial infarction or during digitalis toxicity there is an increase in activity in the cardiac sympathetic nerves [7, 72] This may enhance spontaneous diastolic depolarization in latent pacemaker fibers alter refractoriness in cardiac fibers and result in reentry or enhance the slow inward current in areas where cells have low membrane potentials and thus facilitate reentry DPH decreases the efferent sympathetic activity in the cardiac nerves which may be responsible for arrhythmias accompanying digitalis toxicity [73] This decrease in sympathetic activity results from a depressant effect of DPH on the sympathetic centers in the central nervous system [4] and may be an important antiarrhythmic effect of the drug

V Effects of DPH on the electrophysiology of the *In Situ* Heart

Effects on the SA node When administered to experimental animals or humans DPH has a variable effect on sinus rate which may increase remain unaltered or decrease [8, 75, 7] These effects may be mediated through the autonomic nervous system[76] and may depend on whether the sinus node is normal or diseased That direct effects of DPH on the sinus node action potential probably are not important has been shown in studies on isolated rabbit atria in which the action potential and slope of phase 4 depolarization of sinus node cells were unaltered by a wide range of DPH concentrations [49]

The acceleratory effect of DPH on sinus impulse initiation which has been observed in some instances may be provoked reflexly through alterations in autonomic tone resulting from slight hypotension or pain at the injection site or may be exerted through effects of DPH on the central or autonomic nervous systems which have not yet been described [7] It has been suggested

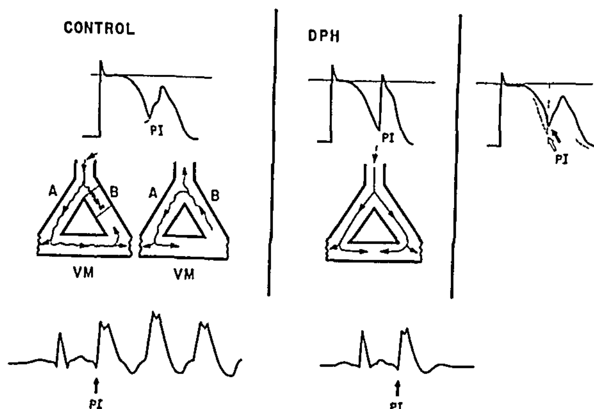


Fig 7 Mechanism by which shortening action potential duration relative to effective refractory period may abolish reentry In the *control panel at the top* a premature impulse *(PI)* arises at the end of the effective refractory period during the repolarization phase of a Purkinje fiber and as a result has a very slow upstroke velocity This premature impulse conducts slowly into a loop of Purkinje fiber bundles *(left middle)* blocks in the antegrade direction in branch *B* and conducts slowly through branch *A* VM and into *B* in a retrograde direction The impulse continues back through *B* as a reentrant depolarization *(right middle)* and then continues to conduct around the loop again At the bottom the ECG is shown the premature impulse *(PI)* that causes the continuous reentry is followed by a run of ventricular tachycardia In the *DPH panel* after administration of DPH the action potential duration of the Purkinje fiber at the top has shortened by 30 msec but the effective refractory period is almost the same Now the earliest premature impulse arises from a higher level of membrane potential and therefore its upstroke velocity is increased This premature impulse conducts more rapidly and activates the Purkinje fiber loop in a normal manner there is no reentry *(middle)* On the ECG at the bottom only the initial premature impulse is seen but it is not followed by ventricular tachycardia In the panel at the right the control action potentials *(solid trace)* and the action potentials after DPH *(dashed trace)* are superimposed Note that the earliest premature impulse after DPH arises from a more negative membrane potential and has a more rapid rate of depolarization than the earliest premature impulse in the control

cacy than DPH in the treatment of atrial arrhythmias, and this may be a result of the marked prolongation in atrial refractoriness produced by this drug [59]

Effects on automaticity Spontaneous impulse initiation may occur either at high or low levels of membrane potential Although the effects of DPH on automaticity have not been investigated with respect to the mechanism for spontaneous impulse initiation, available experimental data indicate that DPH depresses the slope of phase 4 depolarization of both Purkinje fibers with normal maximum diastolic potentials and partially depolarized fibers [52, 54] The increased slope of spontaneous diastolic depolarization induced by catecholamines or digitalis is also depressed by DPH [52] In fibers in which the phase 4 depolarization has resulted in decreases of action potential amplitude and V_m suppression of the slope of diastolic depolarization prior to initiation of the action potential results in an increase in V_m and action potential amplitude [52] This occurs because phase 0 depolarization is initiated from a higher level of membrane potential In this way the DPH induced decrease in the slope of phase 4 may result in an improvement in conduction

Molecular bases for electrophysiologic effects of DPH on cardiac fibers Diphenylhydantoin is particularly effective against the atrial and ventricular arrhythmias which result from digitalis toxicity Such arrhythmias may be due at least partly to digitalis induced inhibition of the active Na -K exchange system in the sarcolemma which pumps Na out of the cell and K

for the slowed ventricular response during atrial fibrillation

The mechanism by which DPH sometimes accelerates AV nodal conduction in the experimental animal and in humans is uncertain Improvement in AV nodal conduction is not seen in the denervated canine heart[76] or in the isolated blood perfused canine heart[34] suggesting that the acceleratory effect is exerted via the nervous system possibly a decrease in vagal activity and not through a direct effect of the drug on the AV node Further clarification of the exact mechanism is required

Effects on the ventricular specialized conducting system and ventricular muscle In the intact or denervated canine heart and in the human heart as well therapeutic and toxic levels of DPH do not significantly slow conduction in the His Purkinje system (do not alter the H V intervals in the His bundle electrogram) nor do they slow conduction in ventricular muscle there is no significant effect of the drug on the electrocardiographic QRS complex[5, 6, 8] This is consistent with the observations that DPH does not markedly depress V_m of phase 0 of the Purkinje fiber or ventricular muscle action potential The effect of DPH on the diseased conducting system is uncertain and caution should be taken when administering the drug to patients with intraventricular conduction defects or bundle branch block because of the possibility of further conduction depression

Even though DPH may sometimes improve V_m and conduction velocity in isolated Purkinje fiber bundles as described above only one study has shown DPH to speed His Purkinje conduction in the intact heart this occurred in the canine heart after conduction had been depressed by toxic concentrations of procaine amide[53]

DPH shortens the relative and effective refractory period and improves conduction of premature impulses in the ventricular conducting system and ventricular muscle in both canine and human hearts[7, 80] This effect is probably due to the shortening of the action potential duration which was described above

DPH will also suppress automaticity of ventricular pacemakers in the intact canine heart Such automaticity can be measured indirectly by determining the idioventricular rate after vagal stimulation has arrested the atria or in animals with complete A V block. DPH has minimal depressant effects on ventricular rate unless it has been enhanced by digitalis[80]

Summary

DPH is highly effective against both atrial and ventricular arrhythmias resulting from digitalis toxicity and should be considered one of the primary antiarrhythmic drugs in this clinical situation Clinical studies have indicated that DPH for the most part is ineffective against atrial arrhythmias and not markedly effective against ventricular arrhythmias associated with acute or chronic cardiac disease For the latter ventricular arrhythmias DPH is usually considered only after other antiarrhythmic drug therapy has failed Studies on the mechanisms responsible for the antiarrhythmic effects of DPH are as yet inconclusive There is good evidence that its actions differ from those of the commonly used drugs with local anesthetic effects The extent to which it exerts direct effects on the heart which are therapeutically relevant remains to be demonstrated further there is solid evidence that its effects on the central nervous system may be of prime importance in its antiarrhythmic efficacy

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that DPH has vagolytic effects, but this sugges tion has been disputed [49]

High plasma levels of DPH which may produce undesirable neurological symptoms usually do not depress the sinus node in patients without sinus node disease However, there have been reports of severe sinus bradycardia or sinus arrest as a toxic response to DPH, although these actions appear to be unusual [77] Preexisting sinus node disease may be responsible for the drug induced depression of sinus node function This is suggested since experimental procedures such as stretch or mechanical trauma, which cause sinus node depression in the isolated rabbit heart, render the sinus node more easily depressed by high DPH concentrations [49] An additional factor to be considered is the commercial solvent for DPH, a solution of propylene glycol and ethyl alcohol with a pH of 11 to 12, which also may depress sinus node function [78]

Effects on atrium It is difficult to determine which of the several electrophysiological effects of DPH on atrial transmembrane potentials demon strated *in vitro* are important for the *in situ* heart DPH does not markedly slow atrial conduction velocity [79] therefore it probably does not signifi cantly decrease V_{max} of normal atrial fibers *in situ* The effect of DPH on atrial refractoriness is uncertain both shortening of atrial refractori ness[80] and no change[75, 76] have been reported Since the commercial diluent for DPH may prolong the effective refractory period, this may obscure any accelerating effect of the drug on repolarization DPH has also been reported to decrease atrial diastolic threshold[80] and to increase it [79, 76] Again the effects of the drug must be separated from the combined effects of drug and commercial diluent

Effects on the AV node Antiarrhythmic concentrations of DPH have a variable effect on conduction and refractoriness of the normal AV node in both experimental animals and in humans DPH often accelerates AV nodal conduction slightly [8, 75, 76, 81, 82] However in some instances no effect or a slight slowing is observed [8, 75] Acceleration of AV nodal conduc tion is not dependent on changes in heart rate since it also occurs when atrial rate is maintained constant [75, 82] Concomitantly, the AV nodal effec tive and functional refractory periods may be reduced but this effect, too, is not invariable [75] Even when large doses of DPH are administered significant depression of AV nodal conduction usually does not occur and therefore this is not a commonly encountered toxic effect of the drug

The acceleratory effects of DPH on AV nodal conduction are more marked in the canine heart after AV nodal conduction time has been pro longed by toxic concentrations of digitalis [81] DPH concentrations which abolish the digitalis induced ventricular arrhythmias consistently reduce AV nodal conduction time under this experimental condition DPH also accelerates AV nodal conduction in the canine heart after it has been slowed by toxic concentrations of procaine amide [83] The lack of deleterious effects of DPH on AV nodal conduction in the setting of digitalis toxicity, and the ability to overcome the digitalis induced impairment of AV nodal conduction in the experimental animal suggest an advantage in utilizing DPH in humans to treat digitalis induced arrhythmias There is no published data to indicate that DPH similarly can overcome digitalis induced AV nodal impairment in hu mans but DPH, unlike procaine amide, does not seem to exacerbate AV nodal conduction impair ment during treatment of digitalis toxic arrhyth mias

The observation that DPH may improve depressed AV nodal conduction in animals does not indicate that DPH should be used as a therapeutic intervention for AV nodal conduction disturbances due to digitalis or other etiologies in humans The effects of DPH, when AV nodal conduction is depressed by disease, is not known Certainly, caution should be utilized in the administration of DPH to patients with diseased AV nodes and depressed conduction since several clinical reports indicate a worsening of AV nodal conduction which may progress to complete AV block in this circumstance [84]

The possibility of an acceleratory effect of DPH on AV nodal conduction suggests that caution should be used if the drug is administered for ventricular arrhythmias in the presence of atrial flutter or fibrillation One would predict that DPH could increase the number of impulses successfully traversing the AV node and therefore increase ventricular rate Clinical experience has actually demonstrated a decrease in the ventric ular response to atrial fibrillations in some patients [11] If DPH in fact accelerates AV nodal conduction, increased concealment of atrial impulses in the AV node may be the mechanism

for the slowed ventricular response during atrial fibrillation

The mechanism by which DPH sometimes accelerates AV nodal conduction in the experimental animal and in humans is uncertain Improvement in AV nodal conduction is not seen in the denervated canine heart[76] or in the isolated blood perfused canine heart [4] suggesting that the acceleratory effect is exerted via the nervous system possibly a decrease in vagal activity and not through a direct effect of the drug on the AV node Further clarification of the exact mechanism is required

Effects on the ventricular specialized conducting system and ventricular muscle In the intact or denervated canine heart and in the human heart as well therapeutic and toxic levels of DPH do not significantly slow conduction in the His Purkinje system (do not alter the H V intervals in the His bundle electrogram) nor do they slow conduction in ventricular muscle there is no significant effect of the drug on the electrocardiographic QRS complex [5, 76, 82] This is consistent with the observations that DPH does not markedly depress V_m of phase 0 of the Purkinje fiber or ventricular muscle action potential The effect of DPH on the diseased conducting system is uncertain and caution should be taken when administering the drug to patients with intraventricular conduction defects or bundle branch block because of the possibility of further conduction depression

Even though DPH may sometimes improve V_m and conduction velocity in isolated Purkinje fiber bundles as described above only one study has shown DPH to speed His Purkinje conduction in the intact heart this occurred in the canine heart after conduction had been depressed by toxic concentrations of procaine amide [3]

DPH shortens the relative and effective refractory period and improves conduction of premature impulses in the ventricular conducting system and ventricular muscle in both canine and human hearts [7, 80, 3] This effect is probably due to the shortening of the action potential duration which was described above

DPH will also suppress automaticity of ventricular pacemakers in the intact canine heart Such automaticity can be measured indirectly by determining the idioventricular rate after vagal stimulation has arrested the atria or in animals with complete A V block DPH has minimal depressant effects on ventricular rate unless it has been enhanced by digitalis [80]

Summary

DPH is highly effective against both atrial and ventricular arrhythmias resulting from digitalis toxicity and should be considered one of the primary antiarrhythmic drugs in this clinical situation Clinical studies have indicated that DPH for the most part is ineffective against atrial arrhythmias and not markedly effective against ventricular arrhythmias associated with acute or chronic cardiac disease For the latter ventricular arrhythmias DPH is usually considered only after other antiarrhythmic drug therapy has failed Studies on the mechanisms responsible for the antiarrhythmic effects of DPH are as yet inconclusive There is good evidence that its actions differ from those of the commonly used drugs with local anesthetic effects The extent to which it exerts direct effects on the heart which are therapeutically relevant remains to be demonstrated further there is solid evidence that its effects on the central nervous system may be of prime importance in its antiarrhythmic efficacy

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Annotations

Hemolysis in Starr-Edwards cloth covered mitral valve prostheses

The first totally cloth-covered Starr Edwards prostheses for the aortic valve (Series 2 300) and for the mitral valve (Series 6,300) were introduced into clinical use in 1967 Since that time these prostheses and their subsequently introduced improved models of the same series have come into wide usage The incidence of thromboembolism has been significantly reduced in comparison with previous models It was soon noted however that in the case of aortic valve prostheses the incidence and degree of hemolysis was considerably increased with the cloth covered series[1] An increase in this complication was not initially reported with the mitral prostheses. Indeed, Starr stated in 1970 that "chronic traumatic hemolytic anemia is unknown after mitral valve replacement with the various model ball valve prostheses except in the presence of perivalvular leak. More recently Crexells and co-workers[a] found an overall incidence of hemolysis of 92 per cent among 36 patients with mitral Starr Edwards totally cloth-covered valves, with 30 per cent showing severe hemolysis In the study of Slater and Fell[1] there was a lower incidence some degree of hemolysis being present in 60 per cent and marked hemolysis (as evidenced by red-cell fragmentation) in 15 per cent of 47 cases of Starr Edwards mitral prostheses the totally cloth-covered model "was used in most cases" in this series.

We studied 14 patients who had undergone mitral valve replacement one-half to three years previously with Starr Edwards protheses, Model 6,310 or 6,320 Plasma hemoglobin serum haptoglobin serum lactic dehydrogenase as well as complete blood count, serum bilirubin serum iron iron binding capacity and urine hemosiderin determinations were performed by the clinical laboratory Peripheral blood smears were screened for the presence of schistocytes by counting 200 erythrocytes In order to rule out the possibility of hemolysis due to factors other than the prosthetic valve the following tests were also carried out electrophoresis of hemoglobin on cellular acetate membrane fetal hemoglobin by the alkali denaturation technique and screening for non ABH red cell antibodies on reference cells in saline and albumin, and with antihuman serum (antiglobulin test) the results were normal in all 14 patients

The results are listed in Table I as well as our assessment of the degree of hemolysis based on these findings. The presence of hemosiderinuria of low serum haptoglobin levels, and increased serum lactic dehydrogenase levels indicate that definite hemolysis is present in all cases The hemolysis is considered marked in one case and moderate in three cases It is to be noted that most of the patients had received oral iron and folic acid therapy at some time which probably explains the absence on severe anemia in any of them nevertheless five of the patients were iron deficient. In none of the cases

Table I

	Hemoglobin (Gm. %)	Hematocrit (%)	Reticulocytes (%)	Schistocytes (per 200 RBC)	Urine hemosiderin	Plasma hemoglobin (mg %)	Haptoglobin (mg %)	L D H (units)	Serum iron (µg/100 mL)	Iron binding capacity (µg/100 mL)	Hemolysis
1	11.7	36	2.8	0	+	12.8	9.4	210	60	332	Moderate
2	16.8	49	1.6	0	+	3.0	13.2	370	85	—	Mild
3	1[illegible].2	38	1.6	1	+	1.7	13.2	396	25	445	Mild with iron deficiency
4	11.2	36	2.6	1	+	2.7	8.8	310	70	415	Mild
5	11.2	36	4.0	1	+	0.9	10.0	360	127	[illegible]87	Mild
6	10.3	3[illegible]	3.0	0	+	5.4	9.1	227	48	373	Mild with iron deficiency
7	11.6	41	1.0	1	+	2.3	9.4	430	48	410	Mild with iron deficiency
8	10.6	4[illegible]	2.6	8	++	7.3	16.4	315	277	5[illegible]4	Marked
9	11.9	35	[illegible]6	2	+	15.0	8.[illegible]	470	35	385	Moderate with iron deficiency
10	1[illegible].5	4[illegible]	1.0	1	+	0.2	10.9	270	66	231	Mild
11	1[illegible].0	40	2.2	2	+	12.3	9.7	360	118	383	Moderate
12	13.6	43	3.0	[illegible]	+	0.8	19.8	480	30	—	Mild with iron deficiency
13	13.8	46	2.6	1	+	2.8	12.0	239	11[illegible]	39[illegible]	Mild
14	13.0	40	1.4	2	+	1.3	11.[illegible]	304	90	270	Mild

was there any clinical evidence of malfunction of the prosthesis

Our findings confirm the definite association of chronic hemolysis with the totally cloth covered Starr Edwards mitral prostheses Although the hemolysis is not usually severe these patients frequently develop iron deficiency which can lead to serious anemia It is to be emphasized therefore that patients with cloth covered mitral prostheses as well as those with aortic prostheses must be carefully followed hematologically Iron and folic acid therapy is necessary in many of the cases in order to prevent anemia which may further compromise their hemodynamic status

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Physician education in cardiopulmonary resuscitation

Cardiopulmonary resuscitation (CPR) is an integral part of emergency medical practice dependent for its widespread application and success upon the skill of both physicians and paramedical personnel (nurses ambulance drivers emergency mobile units etc) Physicians in emergency rooms and coronary and intensive care unit settings are exposed to and well trained in these methods Other physicians for whom the use of CPR is an infrequent and sporadic event are usually less knowledgeable in this area For this reason it seems appropriate that programs of instruction in CPR techniques be provided continuously

Instruction in CPR is usually made available by local and national organizations and is dependent for its success upon adequate physician attendance at their meetings However a larger number of physicians could more easily be reached on a repetitive and frequent basis by means of educational programs within the hospitals in which they practice In an effort to determine to what extent this is being done brief questionnaires were sent to the directors or administrators of hospitals in the state of Connecticut Pertinent questions were (1) Does your hospital have a program of instruction in cardiopulmonary resuscitation for attending physicians? (2) If the answer to question 1 is yes is participation mandatory? (3) Is there a hospital bylaw or regulation concerning this?

Table I analyzes the answers to these questions by hospital size Only those hospitals with a positive reply to question 1 recorded an answer to questions 2 and 3

Responses were received from all 41 of the hospitals to whom the questionnaire was sent (Table I) Fifteen hospitals indicated that there was a CPR training program for attending staff in existence at their institution Twenty six had no such program or did not answer the question although several responses indicated that they were in the process of arranging one In only four hospitals was attendance mandatory in two of which it was apparently a hospital rule or bylaw A few hospitals stated that there was a program for housestaff nurses and emergency teams but none for the attending medical staff A breakdown of hospitals by size revealed a similar frequency of CPR programs in both large and small institutions (Table I) No attempt was made in this survey to analyze program content which varied from sporadic to regularly held meetings utilizing standard demonstration manikins discussions lectures slides and movies

It behooves *all* physicians to be thoroughly competent in

Table I

Hospital size (beds)	CPR program			Attendance mandatory			Hospital bylaw or rule		
	Yes	No	NA	Yes	No	NA	Yes	No	NA
Up to 199	5	9	—	1	4	—	—	5	—
200-399	7	9	1	2	5	—	1	5	1
400 and over	3	7	—	1	2	—	1	2	—
	15	25	1	4	11	0	2	12	1

NA = not answered

the techniques of CPR Indeed one might wonder about the legal accountability of a physician for not knowing this procedure If the occasion arises, it would be expected that the physician in attendance be prepared to manage and probably be in charge of the emergency Be that as it may the purpose of this brief study was to determine to what extent the opportunity was available for physicians to receive instruction in CPR at their local hospitals

This study indicates that almost two thirds of the hospitals surveyed were not providing an educational program in CPR for their attending medical staff In view of the emphasis on teaching these techniques to paramedical personnel any implied lack of leadership knowledge and competence on the part of physicians needs immediate identification and correction. Thus, there is an opportunity for either professional organizations or medical program directors to better utilize hospital resources in the community where a physician practices in order to fill this void Whether this should be a mandatory learning experience needs further careful consideration, although a small fraction of the hospitals replying in this study felt it should be so

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Pacemaker survival for 5 5 years

We have just replaced a fixed rate pulse generator powered by standard mercury zinc batteries after 66 months of continuous operation. To our knowledge this is a *record pacemaker* longevity

Our patient an 80-year-old female has had a permanent pacemaker for complete heart block since 1964 In August 1968 her third pacemaker was replaced by a *fourth, an* asynchronous (fixed rate) Cordis low output unit and attached to the existing transvenous electrode a Cordis wire with a 6 mm. tip (Pulse generators of this type with a current limit of 5 ma were supplied by the Cordis Corporation at the request of the author) Thereafter the patient was followed in the Pacemaker Center in routine fashion *The computer* print-out of the ensuing 5.5 years is shown in Fig 1 On Jan 3 19 4 changes in the pacemaker rate were detected on the trans-telephone monitor confirmed in the Pacemaker Clinic and the pulse generator was replaced On removal, *the output* of the pacemaker was still 2 7 volts into 1 000 ohms sufficient to pace the heart (Table I)

Long term function of implanted *pulse* generators is a major objective of all who are involved with pacemakers One way of achieving this objective is to develop new batteries such as radioisotope fuel cells, *new chemical* cells and rechargeable cells. It is important to note however that a striking increase in battery life can also be achieved by taking

Table I

Pulse generator voltage	Values on insertion	Values on removal
Open circuit	6.5	3 7
1 000 ohms	3 4	2 7
Across heart	1 7	2.3

advantage of all that is known about reducing the current drain of the mercuric oxide zinc cell.

The essential principles in achieving this goal are as follows (1) *use of* small electrodes with an associated low excitation *threshold* (2) use of appropriate low output pacemaker and (3) replacement of the pacemaker at end of life

The electrode tip in this case was not as small as the ones used today A 6 mm. electrode has *an area of 0 50* square centimeters a "ball tip" electrode *such as we* now use routinely has an area of 0 12 square centimeters With these very small *electrodes the* current output of the pulse generator might have been set even lower *and with the* further reduction there might have been even longer pacemaker life

The use of pulse generators with reduced output has already resulted in *important prolongation* of battery life as illus-

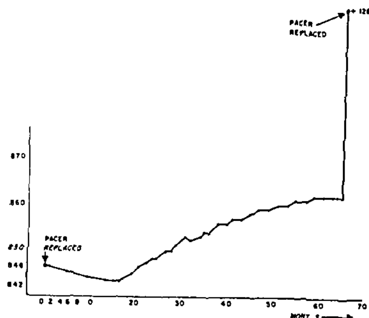


Fig 1 Pacemaker interval as measured in the Pacemaker Center over a period of 66 months Between clinic visits trans telephone monitoring of rate and electrocardiogram were carried out (Graph shows only rate data from clinic There was no significant change in impulse duration and in this instance amplitude measurement was too unstable to be of value)

trated by this case Greater longevity is also reflected by the progressive overall increase of average battery life from 2? to 30 months Results of this type should encourage further studies so that maximum utilization of mercuric oxide zinc and other chemical cells may be achieved

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Of keeping technicians and equipment busy

There is a great tendency for investigators to be concerned about idle technicians and equipment They therefore strive to keep their technicians and equipment busy and are thereby involved with pedestrian research or with merely repeating well established studies with new apparatus Unless there is a new idea involved investigators should not be spinning wheels merely to keep technicians and equipment busy It is expensive to have technicians and apparatus busy and therefore the studies should be worthwhile A careful search of the literature often reveals that new" experiments are decades old Science would advance faster and more effectively if experiments were repeated only when necessary Investigators must realize that they are working when they are thinking and it is creative thinking that really advances knowledge There are many new things to do and to think about There is a distinction between venture research and technologic research The former actually advances knowledge whereas the latter makes use of knowledge

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Letters to the Editor

Energy levels of commercial defibrillators

To the Editor

It has been recently affirmed that commercially available defibrillators cannot consistently defibrillate the ventricles of many animal or human subjects which weigh more than 50 kilograms. The 300 to 400 watt seconds level of energy usually available should therefore be raised in order to be able to defibrillate the ventricles of a greater percentage of patients.

Since our clinical experience seems to be different we would like to know if the above mentioned energy levels concern stored or delivered energy. The question is of great importance.

Energy selectors do not measure directly stored energy but measure the voltage (V) applied to the capacitor. Stored energy (E) is therefore indirectly calculated knowing the voltage and presuming the defibrillator's capacity (C) is a constant ($E = \frac{1}{2} CV^2$) but this latter evidence is far from being real because capacity as happens in any commercial capacitor progressively decreases. Indicated stored energy is therefore less than that effectively stored. Moreover it must be kept in mind that a portion of the not well known stored energy is lost between the capacitor and the paddle electrodes. For these reasons effective delivered energy calibrated to a known resistance is always lower (from ?0 to 80 per cent less) than that indicated by energy selectors.

Is it therefore possible that it is not necessary to raise the energy levels of defibrillators but only to get these devices standardized and periodically checked?

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The ideal artificial heart valve

To the Editor

For many years, there has been a search for ideal artificial heart valves and consequently several types of biological materials and prosthetic devices have been proposed and used



Fig 1 Chest x ray showing the dura mater valve in a patient with an aortic prosthetic valve

Unfortunately each of them has inherent disadvantages which tend to temper initial enthusiasms.

Since January 1971 Dr E J Zerbini and his colleagues in Sao Paulo Brazil have implanted more than 500 mitral, tricuspid and/or aortic artificial valves using human dura mater tissue attached to a Dacron velour ring. The follow up clinical and hemodynamic results are reported as excellent. The low incidence of complications, especially embolic phenomena, provides an encouraging experience for physicians who treat patients requiring valvular replacement.

The dura mater is obtained from previously healthy patients who have suffered accidental death. It is removed at the latest twelve hours after death, and preserved in a sterilized solution of 98 per cent glycerin at room temperature for at least twelve days. Patients who expired from infectious disease degenerative and/or collagen disease, or neoplasm are considered not suitable as tissue donors. After a dura mater strip is sterilized, a tricuspid valve is tailored according to the technique described by Zerbini and colleagues.

The purpose of this communication is to provide the

physician and cardiologist who may encounter such patients with the radiological appearance of the dura mater valve prosthesis implanted by us in the mitral position. The dura mater tissue is radiolucent and only the Dacron strut is seen (Fig 1)

We have begun implanting dura mater valves in either the mitral, aortic or tricuspid positions with alternate patients receiving the Björk Shiley (aortic) or Beall (mitral or tricuspid) valves. We are hopeful of confirming the successful results of the Brazilian group and will provide a statistical comparison with the currently used prostheses. The durability of the dura mater valve has been very promising and the concept of not requiring anticoagulation makes the use of this type of new device very attractive.

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A safe KCl tablet

To the Editor

It is well known that many patients who suffer from heart disease need supplementary potassium and must take potassium chloride in one form or another. Until a few years ago enteric coated KCl tablets were widely used.

It has been proven that taking enteric coated KCl tablets involves some risk—inasmuch as ulcerative obstructive lesions can develop in the small intestines. The theory is that the tablets lose their coating in the alkaline surrounding and thus the KCl is released all of a sudden. It is the high concentration of the drug which affects the mucosa.[1-3] To my knowledge the distribution of enteric coated KCl tablets was discontinued for this very reason.

At the present time patients who need supplementary potassium take it mostly in syrup form. This however has the disadvantage of having a disagreeable taste and it is, therefore, taken reluctantly by most patients. In addition the price of this preparation is relatively high.

To avoid these disadvantages one can alter the coated tablets by a very simple method: at two or three small areas the coating is scraped off the circumference of the tablet with an ordinary file (the type that can be purchased in any hardware store).

When tablets prepared in this manner are swallowed only the flat, still-coated surface of the tablet comes in contact with the stomach lining. The core of the KCl (at the stripped circumference of the tablet) will not touch the membrane at all and therefore will not irritate the mucosa. The diffusion of the gastric juice through the openings of the edge into the core will allow the KCl to dissolve gradually and leak out slowly. Thus, the KCl won't reach the small intestine in high concentration and the cause of ulceration can be avoided.

Tablets prepared as outlined are tasteless and do not cause stomach symptoms of any kind. I have been taking 12 to 15 such tablets daily for many years without experiencing any discomfort. My patients whom I taught to prepare the tablets by this technique take them willingly without any adverse effect. I believe it would be a boon to all patients who need supplementary potassium if KCl tablets with "openings along the edge" could become available.

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Book reviews

The Lymphatic System Revised edition. By Mario Battezzati and Ippolito Donini, New York, 1974 *John Wiley & Sons, Inc* 496 pages Price $37.50

This revised edition of *The Lymphatic System* is a clinically oriented presentation of the lymphatic system These days very little consideration is devoted to lymphatics in under graduate medical education and certainly an insufficient amount of time is devoted to this important aspect of human problems in postgraduate training of physicians There is a tendency to even forget that the lymphatics not only exert a role in the manifestations of peripheral vascular disease but in diseases of other organ systems as well. Those who are most involved with oncology seem to pay more attention to the normal and abnormal states of the lymphatics This book readily displays for the reader the tremendous activity and importance of the lymphatics and lymph in normal and abnormal clinical states Battezzati and Donini ably describe the role of the lymphatic system from the more surgically oriented points of view The English translation is good and the illustrations are numerous and well selected The authors review very well historical, embryological anatomic techni cal and methodological aspects of clinical lymphatology as well as diagnostic technics and disease states of the lymphatic system The lymphatic system of almost all organs and anatomic structures of the body of man are discussed The pathogenesis of disturbances of function and clinical manifes tations of these disturbances are emphasized extensively Methods for visualizing the lymph channels are illustrated and discussed very well The authors have engaged several contributors to assist in the production of this book The book is heavily oriented from the anatomic and physiologic points of view rather than from the diseases themselves This book should be useful to physicians for a knowledge of functional anatomy is of most importance to appreciate disease states of the lymphatic system and the management of these diseases This is a very good book which should prove to be of value to all physicians regardless of specialty

Angina Pectoris Edited by Oglesby Paul New York 1974 MEDCOM Medical Update Series, MEDCOM Press 135 pages.

This MEDCOM issue on angina pectoris follows the tradi tional practical approach of this publication Paul, with the assistance of several contributors, reviews the problems related to angina pectoris Among the subjects discussed are history physiology diagnosis, anginal syndromes psycholog ical and social problems exercise angiography and medical and surgical management The discussions are conventional but practical with the intention of assisting the family physician in managing patients rather than in attempting to assist the cardiologist. Thus the contributors fail to consider controversial issues. For example the treadmill exercise procedure is discussed and on page 79 it is stated that the test should be terminated when the systolic blood pressure exceeds 2?0 mm. Hg and diastolic blood pressure exceeds 135 mm Hg Such levels it would appear to this reviewer would be extremely dangerous and should not be allowed to even be reached in anyone with ischemic heart disease or arterial disease of the brain or disease elsewhere A considerable amount of extremely important benefit in diagnosis should be needed to justify subjecting a patient to such hazardous levels of blood pressure It would seem to be more important to inform readers how to establish a diagnosis of angina pectoris by less dangerous methods of testing Arterial disease is a dangerous disease in itself even at low levels of intravascular pressures. I would suppose the contributors must be dogmatic and precise even though the state of knowledge and data are still inadequate This reviewer has seen patients who have died of cardiac or cardiovascular disease during or shortly after exercise Surely it is impossible to write about any subject that would apply to every individual patient Nevertheless, this issue of *Medcom* is of value to the family doctor who will learn a great deal of useful knowledge provided he is critical in reading the discussions The family physician will like this source of information written by cardiologists who regularly treat patients with angina pectoris

Hypertension Causes Consequences and Management 2nd ed. By Sir George Pickering London 1974 Churchill Living stone 150 pages.

Sir George Pickering has written a small provocative paper back book on hypertension This is the second edition of a condensation of his larger and more detailed book "High Blood Pressure" published in 1968 which contains a great deal of detailed information As did the first edition of the book, this second edition will please the busy physician and student. It is a practical publication of 127 pages of text and an appendix and index Sir George has presented a masterful summary of the present ideas on etiology manifestations complications and treatment of hypertension The various types of hypertension are clearly discussed the coverage of therapy is excellent and the appendix of antihypertensive drugs good This is a highly recommended, lucid and practical publication on hypertension by an expert who writes extreme ly well.

Books received

Prostaglandins from Plexaura Homomalla Ecology Utiliza tion and Conservation of a Major Medical Marine Resource A Symposium Edited by Frederick M Bayer and Alfred J Weinheimer Coral Gables, Fla 1974 University of Miami Press, 16? pp $15 00

Medicaid Lessons for National Health Insurance Edited by Allen D Spiegel, Ph.D., and Simon Podair M D Rockville Md., 1975, Aspen Systems Corporation 375 pp $?4 00

Research in Medical Care British Medical Bulletin Vol 30 No 3, Sept. 1974 London England 1974 The British Council, Medical Dept. price $6.50

The Inflammatory Process 2nd edition vol 1 Edited by Benjamin W Zweifach, Lester Grant and Robert T McClus key New York, 1974 Academic Press Inc price $44 00

Announcements

Purdue Defibrillation Conference

The Biomedical Engineering Center of Purdue University will hold a conference in Lafayette Indiana from October 1 to 3 1975 covering the practical and clinical aspects of cardiac defibrillation The speakers have been selected based upon their positions as leaders in their respective fields The topics to be discussed include clinical basic science and engineering aspects of electrical defibrillation as it pertains to the needs of physicians nurses emergency medical personnel hospital engineers equipment manufacturers and research scientists The state of the art of defibrillation techniques will be presented and examined critically and a major goal of this three day conference will be to integrate all available technology for optimization of ventricular defibrillation The registration fee of $95 includes admission to the proceedings and two luncheons

For further information please write Division of Conferences and Continuation Services Stewart Center Purdue University West Lafayette Indiana 47907 Telephone (317) 749 2533

Tension Control Association meeting

The second meeting of the American Association for the Advancement of Tension Control will be held in Chicago Illinois at the Bismarck Hotel on October 25 and 26 1975 For information write F J McGuigan Ph D Executive Director A A A T C P O Box 7512 Roanoke Va 24019

Mind body self regulation symposium

Biofeedback Meditation and Self Regulatory Therapies a special weekend Symposium cosponsored by Albert Einstein College of Medicine and the Institute for the Study of Human Knowledge will be held at the Roosevelt Hotel New York City on November 22 and 23 1975 Leading researchers will review recent scientific developments in the self control of psychophysiological processes and will assess the therapeutic applications of mind body self regulation in areas such as hypertension cardiac arrhythmias stress syndrome muscular rehabilitation and drug use Included in the program are Neal E Miller Ph D The Rockefeller University New York Herbert Benson M D Harvard Medical School Boston John V Basmajian M D Emory University Atlanta Bernard T Engel Ph D Johns Hopkins University School of Medicine Baltimore Bernard C Glueck M D The Institute of Living Hartford Wolfgang Luthe M D The Oskar Vogt Institute Montreal Arthur K Shapiro M D The Payne Whitney Psychiatric Clinic New York Hospital and Robert F Ornstein Ph D University of California Medical Center San Francisco

Further information can be obtained from Dr Mel Roman Department of Psychiatry Albert Einstein College of Medicine 1165 Morris Park Ave Bronx N Y 10461 Telephone (212) 597 1000 ext 201

American Heart Journal

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Editorial

Echocardiography

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Echocardiography was born in 1954 when Edler and Hertz[1] introduced the reflected ultrasound method for recording cardiac motion Their initial impression that this technic could be applied to the study of mitral valve disease was documented in the subsequent report by Edler and Gustafson [2] Over the next several years interest in this technic was restricted to a relatively few investigators However the validity of the technic for the evaluation of patients with suspected mitral stenosis was confirmed and the method was shown to be reliable for the diagnosis of pericardial effusion [5] About five years ago echocardiography entered a period of remarkably rapid development and acceptance by clinicians This growth spurt continues until today and the pace appears to be accelerating Technics evolved for the ultrasonic visualization of the position and motion of all four cardiac valves and the definition of boundaries of the cardiac chambers and great vessels The result is that echocardiography has expanded beyond the study of mitral valve motion and the detection of pericardial effusion This non invasive tool has been used to evaluate some aspects of left ventricular performance diagnose many types of congenital heart disease and detect intracardiac tumors Investigative efforts in which the reflected ultrasound technic was combined with phonocardiography and catheterization studies have given us a clearer understanding of the mechanism of the production of cardiac sounds and murmurs Rapid research and development in any area of medicine cannot be expected to be free of problems and error This proved to be true during the rapid accumulation of knowledge in the area of diagnostic ultrasound Less than adequate echocardiograms which appeared in the literature in the past were not the fault of the echocardiographer Severe limitations resulted from the inadequacies of the Polaroid film and analog gate method of recording echo patterns The problems inherent in these primitive recording technics have largely been overcome with the introduction of strip chart recorders which give excellent definition and allow the operator to record an unlimited number of cardiac cycles while obtaining M mode scans of the heart In retrospect it is surprising that echocardiography advanced so rapidly while most clinical investigators were restricted to Polaroid film and analog gate recording systems

Unfortunately excellent echocardiographic instrumentation does not insure that one will obtain an excellent echocardiogram or make a correct interpretation of the recording Proper identification of intracardiac echoes can be difficult for even the most experienced echocardiographer This is true even though we were provided with an atlas of echocardiographic anatomy' as a result of the studies in which ultrasonic contrast agents were injected into the heart to define the

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boundaries of cardiac chambers, and insure proper identification of the cardiac valves[6] The difficulties which are encountered in the interpretation of echocardiograms and errors which may result are demonstrated by the large number of *Letters to the Editor*[7] which have pointed out misleading echocardiograms in papers originated from laboratories of very respected investigators There are many examples Improper gain setting has resulted in the epicardial rather than the endocardial echo being shown in published studies of the septal left posterior wall dimension, the left atrial wall has been interpreted as the posterior left ventricular wall and echo patterns from the mitral annulus have been published as representative of movement of the free edge of the anterior mitral leaflet The practical problems of clinical echocardiography have also been apparent to anyone who has attended the many panel sessions on this subject at national meetings over the past few years It is an unusual session if the experts do not have rather spirited disagreement about interpretation of some records It is imperative that the problems and limitations of echocardiography continue to be discussed in the forum of the scientific session and in the medical literature[7] It is likely that the number of Letters to the Editor will decrease since some medical journals are now publishing tiny prints which deny the reader the privilege of determining if the conclusions of the authors are correct I would hope editors would expand the size of the echocardiogram figures and request the authors to constrict the text when necessary to comply with space limitations

While echocardiography has been developing as the result of the attention of a host of clinical investigators new information has produced a continual reassessment of old and new concepts Some of the information on practical clinical echocardiography which was considered absolute truth has had to be revised Echocardiographic patterns which were initially described as diagnostic of an anatomical lesion or hemodynamic abnormality have been shown to lack such specificity Undoubtedly, some new ideas which will appear in the future will also prove misleading or lacking in value for clinical diagnosis An editorial devoted to a large subject such as echocardiography should not and cannot, be a comprehensive review With the hope of arriving at a realistic view of the present state of the art, and an appreciation of what may be expected in the future it does seem appropriate to consider the course of evolution in a few selected areas

The mitral valve and mitral stenosis

Following the demonstration that a reduced rate of early diastolic mitral valve closure was an index of the severity of mitral stenosis,[3,4] it was shown that the width of the anterior mitral leaflet echo was useful in the preoperative assessment of mobility and thickness of the valve[8] The velocity of the diastolic descent appears to be determined by the rate of left ventricular filling and the pressure gradient between the left atrium and left ventricle[9] The validity of the use of the echocardiogram to assess mitral stenosis continues to be accepted without serious challenge However it became apparent that a decrease in the velocity of early diastolic descent was not specific for this valve lesion A reduced rate of diastolic closure was noted in patients with decreased left ventricular compliance and a decrease in the velocity of left ventricular filling as may be present in hypertrophic subaortic stenosis or left ventricular hypertrophy due to fixed left ventricular outflow obstruction[10] Therefore, a reduced early diastolic velocity of the anterior mitral leaflet can no longer be accepted as conclusive evidence for the presence of mitral stenosis The difficulty in differentiating between valvular mitral stenosis and a reduced mitral velocity due to other conditions was largely eliminated when the Indiana group demonstrated the value of recording the echo from the posterior leaflet[11] The anterior and posterior leaflets move in opposite directions in normal individuals and in patients with restricted anterior leaflet motion due to lesions other than mitral stenosis In contrast the leaflets move in essentially the same direction in patients with valve stenosis

Hypertrophic cardiomyopathy

Several years ago, it was shown that the anterior mitral leaflet motion pattern in patients with idiopathic hypertrophic subaortic stenosis not only had a diastolic configuration similar to that seen in mitral stenosis but also a peculiar abnormal anterior movement during systole The systolic anterior motion toward the septum was

recognized as the echographic demonstration of the subaortic outflow obstruction [10] However an anterior systolic motion of the leaflet may be seen in some patients with the mitral valve prolapse syndrome [11] Care must be taken to avoid recording the pattern from near the base of the mitral leaflet in patients with mitral prolapse because this projection is particularly likely to result in a pattern suggesting obstructive cardio myopathy [13] Recent reports indicate that this confusion may be avoided by noting that the late systolic position of the valve is posterior to the C point in the mitral prolapse syndrome and anterior to this point in patients with idiopathic hypertrophic subaortic stenosis [16] The point to be emphasized is that this is another example of the fact that close attention to technic and careful interpretation is required to avoid false informa tion

The echocardiographic demonstration of septal hypertrophy which is disproportionate to the thickness of the posterior left ventricular wall has been described as indicative of hypertrophic car diomyopathy Abbasi and colleagues[17] reported marked thickening of the interventricular septum and only slight increase in left ventricular posteri or wall thickness in patients with non obstructive hypertrophic cardiomyopathy The septum posterior wall thickness ratio was 2 0 or greater [7] Henry and associates reported a ratio greater than 1 3 in a group of patients with asym metrical septal hypertrophy It now appears that this echocardiographic finding should not be considered diagnostic of hypertrophic cardiomy opathy Goodman and co workers [3] found that all 9 of a group of patients with primary pulmonary hypertension had an interventricular septum posterior left ventricular wall ratio greater than 1 3

An abnormality of aortic valve motion has also been reported as a possible aid in the diagnosis of hypertrophic obstructive cardiomyopathy Fol lowing initial systolic opening the cusps move to a closed position in mid systole and reopen in late systole However it would appear that this aortic valve pattern cannot be considered specific for hypertrophic subaortic stenosis Similar aortic cusp echograms have been recorded from patients with discreet subaortic stenosis Further reports will be needed to determine the significance of this abnormal pattern of aortic valve motion

Congenital heart disease

Echocardiography has been used to record mo tion abnormalities which result from distorted hemodynamics of congenital disease such as volume overload of the right heart Also specific anatomical abnormalities have been delineated by the echo technic An abnormal pattern of paradoxical or flat systolic interventricular septal motion was described in patients with atrial septal defects and a left to right shunt [20] In this initial report it was emphasized that this pattern was not specific for an atrial septal defect but could be found in other conditions which produced right ventricular volume overload This technic has distinct value as a screening proce dure However one group of investigators report ed that 5 of 21 patients with atrial septal defects and significant left to right shunts had normal interventricular septal motion [21] Also it has now been shown that abnormal septal motion cannot be considered specifically diagnostic of right ven tricular overload Paradoxical or flat motion is found in some patients with obstruction of the left anterior descending artery and in some patients with left bundle branch block [2, 22] There is evidence that the configuration of the paradox ical septal motion which is due to left bundle branch block is different from the paradoxical pattern found in other conditions In left bundle branch block there is a pronounced abrupt posterior motion of the septum immediately after the onset of the QRS This brief posterior motion is followed by paradoxical anterior septal move ment during the remainder of ventricular systole [22] It appears that this may be a specific pattern for left bundle branch block however further reports may show that this is another concept which must be modified An erroneous diagnosis of abnormal septal motion may occur if care is not taken to insure proper beam direction If the transducer is angled medially and super iorly it will transect the septum near the root of the aorta At this point the septum of many normal individuals will move anteriorly during systole

Abnormal motion of the interventricular septum has been found in most reported cases of Ebstein s anomaly [24, 25] However the most im pressive echocardiographic finding is a delay in closure of the large sail like anterior tricuspid leaflet The amplitude of the tricuspid valve

excursion is increased in many patients, but it is normal in others The early diastolic descent of the tricuspid leaflet is slow in some cases of Ebstein s anomaly, but the velocity is normal in other patients [4, 26] The variability of the tricuspid diastolic descent and excursion probably is the result of the fact that the severity of the anatomical and hemodynamic abnormality varies greatly in patients with Ebstein's anomaly Further studies are needed to determine if the velocity of diastolic descent and amplitude of motion of the tricuspid leaflet may give useful clinical information about the severity of the lesion in the individual patient

Detection of abnormal interventricular septal motion in patients with right ventricular diastolic overload due to congenital heart disease, and the graphic registration of the peculiar motion of the tricuspid leaflet in Ebstein s anomaly are useful applications of the reflected ultrasound technic However these are not true anatomical studies The most valuable application of echocardiography in the diagnosis of congenital heart disease will undoubtedly result from the ultrasonic visualization of anatomical malformations Conventional M mode scanning has been used to depict the distorted anatomy in many forms of congenital heart disease including the hypoplastic left and right heart syndromes single ventricle large ventricular septal defects transposition of the great vessels origin of both great vessels from the right ventricle truncus arteriosus and tetralogy of Fallot [27, 31] In these examinations the scanning technic is used to determine the size of the cardiac chambers the presence or absence of the semilunar and atrioventricular valves the presence or absence of the interventricular septum the spatial relation of the great vessels, and the continuity of the septum with the aorta and the mitral valve with a semilunar valve Although the number of reported cases remains relatively small there is no doubt that M mode echocardiography is now established as a valuable tool in the over all assessment of the child with congenital heart disease The technic has been quite successful in the diagnosis of hypoplastic left or right heart syndromes [27, 30, 33] The early clinical studies suggested that differentiation of a single ventricle from hypoplasia of the right or left ventricle was extremely difficult [27] Subsequently, it has been shown that this differentiation can usually be made, but it may be extremely difficult to distinguish between a single ventricle and L transposition of the great vessels [30, 31] Mitral semilunar valve discontinuity is characteristic of the echocardiogram in patients with a double outlet right ventricle [29] We may anticipate a similar mitral semilunar valve discontinuity in those cases of transposition of the great vessel in which fibrous continuity between the mitral and pulmonic valve is not present [34] The typical echocardiogram in truncus arteriosus shows a single semilunar valve and a large single vessel overriding the ventricular septum It has been emphasized that this pattern should not be accepted as specifically diagnostic of this lesion since differentiation from a tetralogy of Fallot may not be possible [32] A great vessel overriding the ventricular septum may be visualized in both of the abnormalities and it may not be possible to identify the pulmonic valve in patients with tetralogy of Fallot At present it appears that the diagnosis of truncus arteriosus can be excluded if two semilunar valves are detected but the inability to demonstrate the pulmonic valve should not be considered conclusive diagnostic evidence for a truncus arteriosus

The M mode ultrasound pattern can be used to demonstrate the altered spatial relationship of the great vessels in patients with dextrotransposition [31] In this report Gramiak and co workers[31] properly emphasized the deficiencies of M mode scanning in the diagnosis of transposition and other types of congenital heart disease M mode echocardiography is a one dimensional system which visualizes only a narrow portion of the heart The anatomical relationship of adjacent structures is not defined and the recording gives no information regarding simultaneous movement of contiguous structures Also, ' M mode ultrasound anatomy is quite different from the anatomy seen in the dissection room This accounts for many of the errors which have occurred in the interpretation of records Two dimensional echocardiographic instruments should greatly improve the accuracy of diagnosing anatomical abnormalities and may permit a better assessment of left ventricular function Cross sectional ultrasonic images which approximate true anatomy have been obtained with a stop action two dimensional system [35] While not infallible, this system produces images of congen

ital malformations in a more readily understood presentation than is possible with the M mode scan[3] Recently two systems have been devel oped and u ed in clinical trials to record real time two dimensional echocardiograms One system incorporates multiple piezoelectrical elements in a linear configuration[37] The other instrument employs a single transducer for rapid sector scan ning Each system generates several frames each second and gives a time motion representation of the cross-sectional area of the heart which is traversed by the ultrasonic beam It seems reasonable to anticipate that these systems will greatly expand the use of echocardiography in the diagnosis of congenital disease and may well improve the accuracy of detecting regional areas of abnormal left ventricular contraction One disadvantage is that the individual frames lack the definition of echo patterns obtained with the conventional M mode instruments We have had limited experience with the multiple element real time two-dimensional ultrasound system in our laboratory Lesions such as prolapse of the mitral leaflet can be demonstrated much more easily than is possible with conventional M mode recordings and the character of the posterior ventricular wall movement can be visualized quite well However we have not been convinced that we have been able to obtain information which we are unable to obtain with M mode scanning in the adult patient However it seems likely that the two dimensional real time echo cardiography will become the most desirable echocardiographic technic for the diagnosis of congenital heart disease in children

Left ventricular function

Interest in echocardiography rapidly escalated when it became apparent that this method could probably be employed for the non invasive assessment of some aspects of left ventricular function Reports from many investigators showed a rela tion between a ventricular septum left posterior wall dimension and angiographically determined left ventricular volume[3] [3] Changes in this left ventricular dimension during systole and diastole were used to estimate the ejection fraction the stroke volume and mean rate of circumferential fiber shortening [1] [4] It is not easy to master the technic of recording a standardized proper echo cardiogram from the left side of the interventric ular septum and the endocardium of the left ventricular posterior wall Also there are obvious inherent limitations in attempting to derive volumes from a single dimension of a complex cardiac chamber This fact was stated in one of the earliest publications[42] and has been con firmed in subsequent reports The measurements may be in error when there is left ventricular asynergy or distortion of the normal geometry of the left ventricle which alters the usually assumed 2 1 ratio of the left ventricular long axis to the transverse diameter [5] [46] Also reliable esti mation of the stroke volume and ejection fraction cannot be accomplished when there is paradox ical motion of the interventricular septum in patients with right ventricular diastolic overload disease of the left anterior descending artery or left bundle branch block Meticulous attention to technic which is required to perform these studies and inherent limitations of the method have recently been reviewed[4] If the examination is done with care and if one is aware of these limitations echocardiography has real value for the non invasive estimation of performance of the left ventricle The value of this use of echocar diography should not be minimized and the problems should be recognized rather than exag gerated

Summary

We have discussed the evolution of selected areas of echocardiography in an attempt to illus trate the capabilities and limitations of this method of study As information has accumu lated some concepts of the specificity of certain echocardiographic patterns have had to be re vised Awareness of the potential for false positive and false negative results has increased rather than decreased the usefulness of the echo method Equipment deficiencies which existed in past years have largely been corrected thereby reducing the likelihood of repeating some of the earlier mistakes Two years ago we suggested that more patients with left ventricular disease should be studied, the results from different laboratories should be compared a larger number of patients with congenital disease should be evaluated and the limitations of the technic be more precisely defined [3] Obviously much has been accomplished in all of these areas Much more can be done There is every reason to believe

that the next few years will bring many new and important developments in diagnostic echocardiography

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Clinical communications

Electrical axis and voltage criteria of left ventricular hypertrophy

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There are many voltage criteria for left ventricular hypertrophy but those of Sokolow and Lyon[1] are well established and form the basis of those criteria described in the Minnesota code[2] The maximum spatial QRS voltage decreases with age[3] and it is therefore not surprising that all voltage criteria are less specific and more sensitive in younger age groups

The limb lead criteria of Sokolow and Lyon[1] are more specific than the precordial voltage criteria they proposed ($S\ V_1 + R\ V_5$ or $R\ V_6 \geq 37$ mm)[4] Voltages of the limb leads are affected by the electrical axis, however and these criteria are of different significance in the presence of left anterior hemiblock[5]

This study was therefore undertaken to determine the influence of the axis on the voltage criteria of Sokolow and Lyon[1]—namely, the voltage in Lead $aV_L \geq 11$ mm and the voltage in Leads V_5 or $V_6 \geq 27$ mm Other factors that influence the axis have also been assessed since they may have an important effect on these voltage criteria

Materials and method

I studied patients who were being treated for hypertension and attending the Sheffield hypertension clinic from October, 1973, to March, 1974 I examined the electrocardiogram (ECG) before and after treatment for 4 years Twelve patients with left bundle branch system block and 10 patients with right bundle branch system block at some time during this period were excluded and the remaining 229 patients have been reported

The voltage of the S wave in Leads V_1 and V_2 the R wave in Leads V_5 and V_6 and the R wave in Leads aV_L, I, II, and aV_F were measured The heart rate, the electrical axis, the duration of the QRS and any other ECG features were determined In addition, the systolic and diastolic pressures in the lying and standing positions, and the age, sex, and weight of each patient were recorded Means and standard deviations of electrical axis have been calculated by the method of Liebman and co workers[6] Particular note was made of all patients with radiological evidence of cardiomegaly (a cardiothoracic ratio > 1 2) and those with left anterior hemiblock[7] The latter diagnosis was made if the axis was more negative than −30, if there was a q wave and a terminal R wave in Lead aV_L and if there was a terminal S wave in Leads II, III and aV_F

I also took the opportunity of examining the ECG's of 62 untreated hypertensive patients taken over a 4 year period These patients were first seen between 1948 and 1958 and have previously been reported[4, 8] but, in view of the advances in electrocardiography since this time, it was felt that a further examination would be of value Identical measurements were made to those in the treated group

From the voltage criteria patients were classified as having no voltage criteria, limb lead voltage criterion (R in Lead $aV_L \geq 11$ mm), V lead voltage criteria (R in Leads V_5 or $V_6 \geq 27$ mm) or both V and limb lead criteria[1] Such criteria were related to the axis of the ECG the presence of cardiomegaly and the age and sex of the patient

Results

There were 119 men and 110 women in the first group of patients undergoing treatment for hypertension and of these 16 (7 0 per cent) had left anterior hemiblock at some time during the 4

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Table I Voltage criteria of left ventricular hypertrophy and related measurements in patients with hypertension

Criteria	*No*	*Axis*		*Cardio megaly*	*Mean standing systolic pressure (mm Hg)*	*Mean standing diastolic pressure (mm. Hg)*	*Average age (yr)*
		Mean	*S D*				
R in Lead aV ≥ 11 mm.	61	+1 9?	± (17 0)	36	207.3	114 7	53.8
R in Lead aV ≥ 11 mm. and R Leads V or V ≥ 27 mm	15	+5 4	± (19 7)	6	211 0	123 1	52.9
R in Leads V or V ≥ 27 mm. only	13	+8.3	± (?2 ?)	8	238 8	125.3	56 5
None of the above criteria	124	+20 1	± (27.9)	33	208.3	121 7	51 1
Total	?13	+13.3	± 24.3	83	210 0	120.9	52.3

year period Fifteen patients had left anterior hemiblock initially and in five patients it persisted one further patient developed left anterior hemiblock after 2 years of treatment Left anterior hemiblock was more frequent in men than women (11 5) The supine and standing blood pressure levels were similar to those of the patients without hemiblock but the average age of the patients was slightly higher (61 4 S D 24 2)

The remaining 213 patients are described in Table I and have been divided into subgroups according to voltage criteria at presentation Although the lying and standing blood pressures were higher in those patients with V lead voltage criteria alone there were no significant differences between the average blood pressure levels of these subgroups The average age and weight of the patients in these subgroups were also not significantly different It is also apparent from this table that the axis was more negative in patients with the limb lead voltage criteria than in those with V lead criteria or no criteria at all The limb lead criterion was significantly more frequent in patients with cardiomegaly than in the whole group ($p < 0 01$)

The relationship of the aV_L criterion to cardiomegaly and a horizontal axis was further explored (Table II) This confirmed that the axis was significantly more negative in patients with an R wave ≥ 11 mm in Lead aV_L than in patients without such a voltage both before and after treatment Cardiomegaly was significantly more frequent in patients with such limb lead voltage and this was also found after treatment for 4 years Even in the absence of cardiomegaly however the axis was more negative in patients with such limb lead criteria compared to those with only V lead criteria or none at all (Table III) As expected there was a significant difference in axis between the total group with cardiomegaly and the group without cardiac enlargement This relationship was preserved after treatment despite similar blood pressure levels in patients with or without cardiomegaly

In order to confirm that these results were consistent with the general hypertensive population and to observe the effect of untreated hypertension over a 4 year period similar measurements have been presented for the group of untreated hypertensive patients

There were 36 women and 26 men in this study Four men and two women had left anterior hemiblock at some time during the 4 year period (9 6 per cent) Five patients had the hemiblock initially which persisted and one patient developed it after 1 year The remaining 56 patients are described in Table IV The most noteable feature was the association of combined V lead and limb lead criteria with a normal heart size After 4

Table II Differences in the axis and frequency of cardiomegaly in hypertensive patients with and without $R \geq 11$ mm

	No	Initial axis Mean	Initial axis SD	Axis after treatment Mean	Axis after treatment SD	Cardiomegaly
R in Lead $aV_L \geq 11$ mm (± R V or V ≥ 27 mm)	76	+2.6	± 17 3	0 0	± 20.9†	42‡
R in Lead $aV_L \leq 10$ mm (± R V or V ≥ 27 mm)	137	+19 0	± 26 7	+16 0	± 32 7†	41‡
Total	213	+13.3	± 24 3	+10 7	± 29 7	83

t = 4 74 (p < 0 01)
†t = 3 78 (p ≤ 0 01)
‡χ = 12 1 (p ≤ 0 01)

Table III The average axis in association with different voltage criteria of left ventricular hypertrophy with or without cardiomegaly

Criteria	No	Axis	SD
R in Lead $aV_L \geq 11$ mm			
No cardiomegaly	25	+6 5	17.2
Cardiomegaly	36	−1.5	16 8
R in $aV_L \geq 11$ mm and R V or $V_4 \geq 27$ mm			
No cardiomegaly	9	+6 6	23 3
Cardiomegaly	6	+3 6	14 5
R in V or $V_4 \geq 27$ mm only			
No cardiomegaly	5	+15 0	28 9
Cardiomegaly	8	+5 1	20 7
None of above voltage criteria			
No cardiomegaly	91	+20 6	28 0
Cardiomegaly	33	+18 7	33 0
Total without cardiomegaly	130	+16 6	26 0
Total with cardiomegaly	83	+8 2*	21 5

t = 3 56 (p < 0 01)

years the development of cardiomegaly was usually associated with the loss of the V lead criteria but preservation or accentuation of the limb lead voltage in Lead aV_L Some patients who developed cardiomegaly over 4 years showed increased voltage of Lead aV_L, although usually the voltage decreased The initial axis was directed more to the left than normal (+ 40° between 40 and 60 years of age)[5, 10] After 4 years the axis had become significantly more negative in both patients with and without cardiomegaly There were no significant changes in the weight and blood pressure levels of either group during the 4 year period but the patients were on average younger than the patients currently under treatment in the hypertension clinic

All abnormalities of the T wave and ST segment were more frequent in patients with cardiomegaly as were abnormalities of the P wave—for example, P mitrale and a P wave breadth of > 120 msec All these abnormalities often regressed after treatment and reduction in size of the heart

Discussion

It is well known that the axis is more horizontal in patients with hypertension, with or without left ventricular hypertrophy, than in normal persons [10]

This study has shown that the unipolar limb lead criterion of left ventricular hypertrophy (R in Lead $aV_L \geq 11$ mm) is more frequently found in association with cardiomegaly than expected by chance Also the axis is significantly more negative in patients with cardiomegaly It is not surprising that the aV_L lead voltage criterion is usually associated with a horizontal or left axis as was found in this study I also found, however that the axis is more positive if V lead criteria' are present whether the aV_L lead criterion is present or not These associations persisted whatever treatment was given

The axis becomes increasingly negative with age and increasing weight[10] but these factors were no different in each subgroup and cannot have affected the results significantly Although there were slightly more women th in men with the aV_L voltage criterion and more men with the V lead criteria, similar relations of axis to cardiomegaly and to voltage criteria were found if men and women were considered separately The axis is slightly more horizontal in women below the age of 40 years[5, 10] and this may increase the normal

Table IV Voltage criteria of left ventricular hypertrophy in untreated hypertensive patients over 4 years*

	Cardiomegaly initially		*No cardiomegaly initially*	
	No initially	*No later*	*No initially*	*No later*
R in Lead $aV_L \geq 11$ mm	5	8	5	18
R in Lead $aV_L \geq 11$ mm and R Leads V or V ≥ 27 mm	2	0	7	1
R in Leads V or V ≥ 27 mm only	2	2	1	1
None of above criteria	17	16	17	10
Total number	26		30	
Mean age	41 7 (9.9)		47 0 (8 4)	
Mean axis	+ 26 4 (31 6)†	+ 12 4	+ 28 1 (25 8)†	+ 18 9

*Standard deviations are in parentheses
†Significant change of axis after 4 years (t test $p < 0.01$)

voltage in Lead aV_L, but over this age the axis becomes more horizontal in men than in women[5] It therefore appears that there is a direct association between cardiomegaly and a horizontal axis

Dilatation of the heart may produce a reduction of voltage[1] and this has been explained by reduction in thickness of the left ventricular wall Such a reduction of maximum spatial QRS voltage would be expected to affect both V and limb leads Unipolar V leads record both local electrical events from the underlying myocardium and more distant depolarization whereas the limb leads record only distant effects It is therefore likely that V lead voltage will be reduced more than limb lead voltage by cardiac dilatation The left ventricle enlarges to the left and posteriorly and this may rotate the axis to the left.[2] Any such rotation will naturally increase the voltage in Lead aV_L Therefore the development of cardiomegaly may reduce V lead voltage and preserve or accentuate limb lead voltage This will occasionally affect voltage criteria

I have confirmed by voltage measurements over 4 years in both treated and untreated hypertensive patients that the disappearance or development of cardiomegaly is associated with the changes of axis and limb lead voltage that would be expected from the preceding hypothesis

Although it appears that cardiomegaly is an important determinant of the axis it is not the only factor since the axis was more negative than expected in patients without cardiac enlargement and the axis moved to the left over a 4 year period in these patients The axis usually becomes more negative with age[9] and the change in both treated and untreated patients is compatible with the sharp decrease in the axis that occurs over the age of 40 years[10] Other investigators[5] have found that the axis is related to the level of blood pressure when other factors such as the age sex and weight have been taken into consideration Since such studies were performed before the significance of the hemiblocks was appreciated it is possible that marked left axis deviation in a few patients could have affected the results

Left ventricular hypertrophy is usually associated with a more horizontal axis than normal although left axis deviation is unusual.[12] [3] It is difficult to dissociate left ventricular hypertrophy from associated features like obesity and coronary artery disease[1] and therefore it is not known if left ventricular hypertrophy itself rotates the axis to the left Grant[13] considered that left axis deviation with left ventricular hypertrophy was due to the development of left ventricular conduction defects and the concept of the hemiblocks has confirmed this opinion[1] This study has shown that left anterior hemiblock is a relatively uncommon complication of hypertension Like right and left bundle branch system block left anterior hemiblock may disappear with treatment and also develop in both treated and untreated hypertensive patients However it differs from left bundle branch system block since it does not come and go during a period of observation or treatment We have not observed that development or disappearance of these

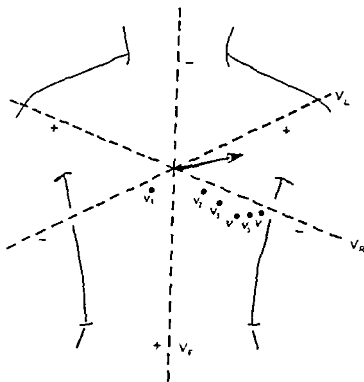


Fig 1 The position of the V leads in relation to the frontal axis Superior direction of the maximum spatial QRS voltage also diminishes the R wave voltage in V and V and may produce an S wave

blocks was related to blood pressure control Although it has been suggested that these conduction defects are due to septal hypertrophy, *they may also be due to associated ischemic heart* disease

This study confirmed that ECG features bear little relation to the level of blood pressure (both with and without treatment) [8, 9] Thus, although *the blood pressure was slightly higher in patients* with voltage criteria of left ventricular hyper trophy and those patients with cardiomegaly, the ECG does not seem of great prognostic value It is remarkable that there is little association *between cardiomegaly and voltage criteria of left* ventricular hypertrophy, although the blood pressure is usually higher when they are both present Cardiomegaly occasionally developed in untreated patients and regressed in treated patients *but usually there was no change in* cardiac size These anomalies reflect our igno rance of the factors which influence the develop ment of left ventricular hypertrophy and cardiac dilatation In particular the duration of hyper *tension is usually unknown*

I have not reported other limb lead criteria of left ventricular hypertrophy[15] because the volt ages in the other limb leads are closely related to that in Lead aV_L[1] and conclusions gained from such leads can be deduced from those reported These leads should, however, always be examined since the unusual presence of a vertical axis may *make them, rather than* aV_L, suggestive of left ventricular hypertrophy I have also not de scribed the combined V lead voltage criteria[1] ($S V_1$ plus $R V_5$ or $R V_6 \geq 37$ *mm*) *Unlike the* R wave voltage in Lead aV_L normal variation of V lead voltage is marked [5, 16] and it is known that the predominant voltage in each of these V leads decreases with age It was therefore suspected *that this criterion and the* S wave voltage in Leads V_1 or V_2 alone would be too variable to be of value This was confirmed by analysis of the *untreated hypertensive patients Despite increas ing* T wave changes over a 4 year period and increasing voltage in Lead aV_L voltage criteria decreased as the voltage of the S wave in Lead V_1 (together with S V_2) and the voltage of the R *wave in Lead* V_5 *decreased The voltage of the* R wave in Lead V_6 on average showed a slight increase Decrease of R wave voltage of Leads V_5 or V_6 was associated with rotation of the axis to the left Thus it is common for these combined criteria to be present in youth and yet disappear with age, despite increasing left ventricular hypertrophy due to hypertension [17]

The limb lead criteria of Sokolow and Lyon are inaccurate in the presence of left anterior hemiblock because rotation of the axis superiorly accentuates the voltage in Lead aV_L It has been found, however, that a voltage in Lead $aV_L \geq 16$ *mm is very suggestive of left ventricular hyper* trophy even in the presence of left anterior hemi block [5] The presence of left anterior hemiblock necessarily decreases the sensitivity of limb lead voltage criteria but it is often not appreciated *that left anterior hemiblock also* decreases the sensitivity of the V_5 and V_6 criteria of left ventric ular hypertrophy This is because the V leads (and Lead X of the modified Frank orthogonal system)[1] are situated below the 0° axis There *fore, if the axis is negative* the maximum spatial QRS voltage is rotated away from the V leads (Fig 1) Even if the axis is more positive than −40° the V lead voltage will be reduced This may explain the occasional loss of V lead voltage and voltage criteria in untreated patients because of the shift of axis to the left Rotation of the *transitional zone to the left due to enlargement of* the heart posteriorly may similarly reduce the

voltage in Lead V_5 and therefore Lead V_6 (which then corresponds to Lead V_5) may be increased

It is also well known that marked rotation of the heart anteriorly or posteriorly reduces the voltage in the frontal plane[11] This was not observed in this study but rotation posteriorly will occasionally eliminate both V lead and limb lead criteria and highlights the importance of multiple leads [5]

Cardiomegaly has been used as an independent sign of left ventricular hypertrophy[11] but it really only reflects cardiac dilatation It is important to recognize the importance of axis changes and cardiomegaly on ECG criteria of left ventricular hypertrophy Thus increasing cardiomegaly may be associated with a loss of V lead voltage criteria and if a small increase in limb lead voltage is not appreciated increasing left ventricular hypertrophy may be missed and even improvement suspected

Summary

The voltage criteria of left ventricular hypertrophy were studied in 229 hypertensive patients undergoing treatment and 62 patients who were not treated The limb lead voltage criterion (R Lead $aV_L \geq 11$ mm) was found more frequently in patients with radiographic evidence of cardiomegaly than other voltage criteria This may have been due to a more negative axis in patients with cardiomegaly than in patients without cardiomegaly It is possible that dilatation of the left ventricle to the left and posteriorly accentuates limb lead criteria at the expense of V lead criteria

Left anterior hemiblock occured in less than 10 per cent of the hypertensive patients In 10 out of 16 patients with left *anterior hemiblock* the hemiblock disappeared after treatment of the hypertension for 4 years whereas all five hemiblocks in *untreated hypertensives* persisted Development of left anterior hemiblock subsequently occurred in only one patient with treatment and one *without treatment* over a 4 year period

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Wenckebach A-V block A frequent feature following heavy physical training

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The physical activity required of a top athlete is far beyond that performed by ordinary people even those whose occupation is mainly physical This activity may cause anatomic and physiological changes sometimes difficult to classify as either normal or pathological In the cardiovascular system hypertrophy of the myocardium and an increase of the vagal tone occur These changes are manifested mainly by bradycardia A first degree heart block is occasionally found

Our interest in a systematic search for conduction disturbances in athletes was aroused by the finding of a Wenckebach type of heart block in a top athlete Our impression was that the conduction disturbances in healthy top athletes are much more frequent than hitherto described, and that even second degree heart block is not rare

A total of 126 athletes from Israeli national teams (swimming, athletics, gymnastics and volley ball teams) were examined A complete physical examination and electrocardiogram (ECG) tracings were performed The ECG was taken after a complete rest of 15 minutes duration in a recumbent position Eleven cases of first degree heart block (P R interval $\geq$ 0 21 sec) were detected, in three of them Wenckebach s phenomenon was also found The conduction disturbance displayed a remarkable correlation with the intensity of training

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Case reports

Case 1 D R a 22 year old swimmer with no medical history had been very active since the age of 12 For the last 3 years prior to examination he had noticed periods of irregular pulse at rest

He was seen in October 1967 At that time he was training intensively for the annual national competition Results of a physical examination were normal the heart rate was 50 beats per minute the blood pressure was 130/70 mm Hg Atrial sounds were heard A chest x ray was normal The ECG revealed sinus rhythm with Wenckebach s periods (Fig 1 A) There were voltage criteria of left ventricular hypertrophy Normal 1 1 conduction with P R interval of 0 24 was resumed upon standing Bicycle exercise produced sinus tachycardia with a P R interval of 0 12 sec

In April 1968 when the intensity of his training was markedly reduced the heart rate was found to be regular at 60 beats per minute and the ECG revealed only first degree heart block with marked prolongation of the P R interval (Fig 1 B)

In April 1969 following a period of intensive training Wenckebach periods were noticed again in the ECG (Fig 2) This phenomenon was abolished by standing when a normal 1 1 conduction was resumed with a P R interval of 0 22 sec During bicycle exercise (of 250 watts intensity) the heart rate was 140 beats per minute with a P R interval of 0 12 sec (Fig 2) Thirty minutes after the end of the exercise he again displayed Wenckebach periods At this point he was given 0 5 mg of atropine subcutaneously Within 10 minutes normal 1 1 conduction was resumed without increase in the sinus rate The P wave became taller and somewhat sharper The P R interval was 0 17 sec (Fig 2)

Case 2 R E was a 23 year old champion volley ball player with no medical history A slow irregular pulse had occasionally been noted previously (March 1967) He was examined once during an intensive athletic training program and three times during periods of much lighter activity The first examination was essentially negative except for periods of Wenckebach type A V block (Fig 3) Standing and exercise restored 1 1 conduction (Fig 4) On his last visit (October 1972) he was less active in sport because of nonmedical reasons and the physical examination and chest x ray were completely negative with no conduction disturbance

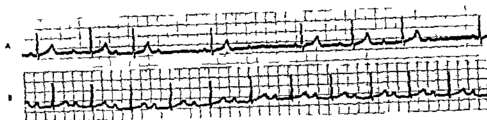


Fig 1 Case 1 A ECG (V) taken at complete supine rest during a heavy training season (atrial rate 60 per minute ventricular rate 50 per minute) B 1 1 conduction during light training season at complete supine rest (ventricular rate 75 per minute P R 0 36 sec)

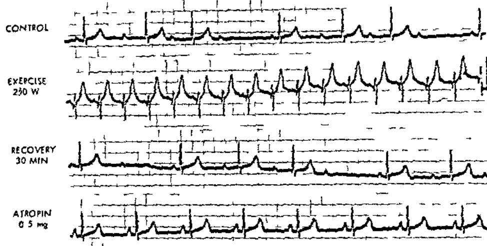


Fig 2 Case 1 ECG (V) (1) at rest in supine position (atrial rate 60 per minute ventricular rate 50 per minute) ( ) during exercise of 250 W (P R 0 12 sec H R, 135 per minute (3) 30 minutes after recovery (4) immediately after the administration of 0 5 atropin (H R 60 per minute P R 0 17 sec) Note the disappearance of the Wenckebach heart block with exercise and atropin

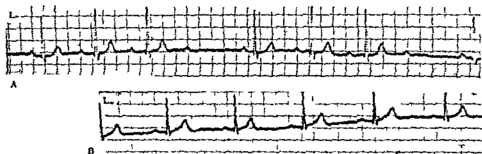


Fig 3 Case 2 ECG s taken at supine rest A Wenckebach during a heavy training period (ventricular rate 55 per minute atrial rate 6 per minute) B 1 1 conduction is present after reducing training intensity (H R 58 per minute P R 0 1 sec)

Case 3 U V a 22 year-old champion middle and long distance runner had been active in athletics since the age of 14 Past and family histories were negative He was seen in November 1968 For the preceding 18 months he had been training intensively (including a daily run of 15 miles)

The physical findings were normal The blood pressure was 150/90 mm Hg. An atrial sound was heard on auscultation Chest x ray revealed enlargement of the cardiac silhouette The ECG showed Wenckebach periods with abnormal P waves (Fig 5 A and B) The P wave was positive in Leads aVR V and V, and negative in Leads I II aVF aVL, and V to V The P vector axis was + 120 in the frontal plane (Fig 6 A) Standing and bicycle exercise produced 1 1 conduction A gradual "normalization of the P wave was noted during the exercise (Fig 6 B) He finished 6 minutes of 350 watts exercise with a heart rate of 180 per minute and a P R interval of 0 15 sec The abnormal P waves reappeared within few minutes of recovery

On Feb 18 1969 he was seen again this time following a complete cessation of physical training for 2 weeks because of

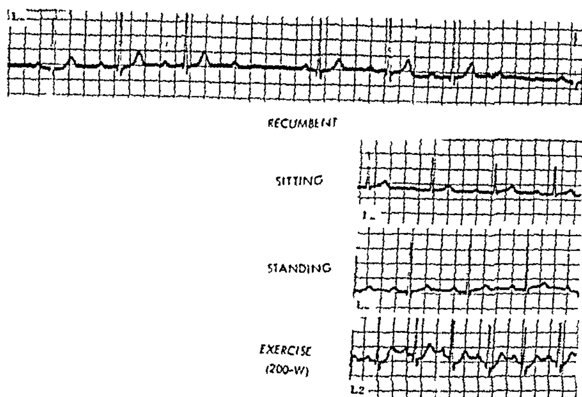


Fig 4 Case 2 Effect of changes in posture and of exercise on the conduction disturbances present at rest Note Wenckebach heart block at supine rest First degree heart block upon sitting (P R 0 26 sec) with normal P R interval induced upon standing (P R 0 20 sec) and exercise (200 W P R 0 16 sec)

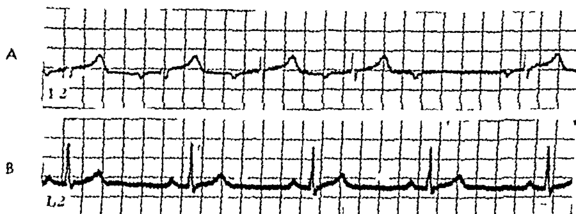


Fig 5 Case 3 ECG taken at complete supine rest during heavy training period (A) and after 2 weeks of rest (B) Note changes from second degree to mild first degree heart block (P R 0 21 sec) and the alteration in the P wave vector

a leg pain Physical findings were unchanged No reason was detected for the leg pains Heart rate was regular The ECG showed normal P waves with 1 1 conduction The P R interval was 0 21 sec (Figs 5 B and 6 B)

Shortly after his previous visit in May 1969 he resumed intensive training The resting ECG again showed the abnormal P waves and Wenckebach periods

Three months later following a period of very light training the ECG again demonstrated a 1 1 conduction with a P R interval of 0 21 sec but on continuous monitoring after 20 minutes of complete rest the P wave (recorded in Lead II) became negative with a 1 1 conduction and without further prolongation of the P R interval This change lasted for at least 15 minutes after which he was disconnected from the ECG

On his last visit in October 1972 while under moderate training a 1 1 conduction with a normal P wave vector was present with a heart rate of over 60 beats per minute With slower heart rates the P wave changed in a similar manner as described above During the years of follow up a slight impairment of his competitive performance could be noticed at times when a Wenckebach type of heart block was present

Discussion

The occurrence of a second degree heart block is almost invariably a sign of drug effect or of organic heart disease[1] Reports describing Wenckebach's periods in a normal population are rare In two large series it was detected in only three out of 67 375[2] and in 1 out of 19 000 people[3]

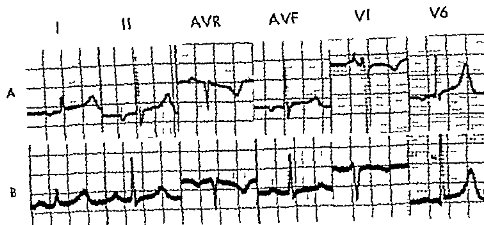


Fig 6 Case 3 Comparison of the ECG taken at rest during heavy training season (*A*) and during light training season (*B*) Note the "normalization" of the P wave upon reduction of training intensity

Out of 32 documented cases of Wenckebach s phenomenon without detectable organic heart disease gleaned from the literature[4, 9] the block could be related to physical training in half of the cases[4,6,9,15,2] but only in 10 of them were details given Of these cases six were in their twenties[7, 15, 22] and the ages of the other four were 36 41 52 and 53 This led Cullen and Collin[13] and Grimby and Saltin[6] to postulate that the conduction disturbance was somehow related to the performance of a strenous exercise by elderly people In trained athletes Wenckebach s A V block has rarely been found[2, 4, 23] In two extensive surveys of ECG abnormalities in athletes which comprised about 4 000 subjects this aberration was found in only seven individuals the estimated frequency having been 0 15 and 0 21 per cent respectively No additional information concerning age training rest and posture was provided

The findings in three of our 126 subjects suggest that if sought under appropriate conditions the frequency of this phenomenon in top athletes is much more common than previously reported In these three athletes the appearance of Wenckebach periods at complete rest was strongly associated with the intensity of the physical training carried out during the same period of time Reduction in the level of training even without complete cessation was sufficient for the second degree heart block to disappear The phenomenon could be demonstrated only after a rest period in a recumbent position of 15 minutes and was abolished by sitting or by standing Therefore it would have been overlooked if these precautions had not been observed

An additional point of interest is the peculiar morphology of the P waves in case 3 (Figs 5 *A* and 6 *A*) The appearance of this abnormal P wave was associated with the intensive training periods and the Wenckebach type of block This phenomenon might be related to a nonhomogenous distribution of the vagal nerve endings within the atrial myocardium A strong cholinergic stimulus may thus favor the development of a nonuniform excitability and recovery[2, 22] It is possible that the pacemaker location was shifted to areas such as the coronary sinus the upper A V nodal region or the left atrium

Patient 3 displayed also a slight impairment of his competitive performance during the periods of ECG abnormalities therefore this conduction disturbance could be the ECG counterpart of the ill defined overtraining syndrome

Conduction abnormalities related to training effect include sinus bradycardia sinus arrhythmias and a prolongation of the A V conduction Altered balance of the autonomous nervous system is most probably the basis of these phenomena[7, 1, 2, 22] In line with the functional as opposed to the organic basis is the finding of Wenckebach s phenomenon in mentally ill patients without heart disease[7, 13] The physiological and benign nature of this finding is manifested in our athletes by (1) its remarkable relationship to training (2) the fact that even a change of posture was sufficient for its abolition (3) the occurrence in young top athletes with the best performance status (4) the follow up period of 6 years during which no change in their health status occurred Nevertheless a much longer follow up period is needed to prove whether the

athletes who exhibit second degree heart block during training are subjects with an occult abnormality of the conduction system which may eventually become permanent The recognition of the functional characteristics of this conduction disturbance in athletes is important for proper clinical evaluation and the avoidance of unnecessary restrictions

Summary

Among 126 top Israeli athletes, in whom an ECG was obtained during a random survey, 11 had first degree heart block (P R $\geq$ 0 21 sec) and in three of them Wenckebach's phenomenon was found The latter could be demonstrated only after 15 minutes rest in a recumbent position and was abolished by sitting standing and the administration of atropine The subjects with Wenckebach s phenomenon were followed for 6 years The heart block was found to be present only during seasons of intensive training and could not be demonstrated a few weeks after the training was reduced in intensity or stopped No heart disease or diminution of performance developed during 6 years of follow up Transient second degree heart block in top athletes is probably much more frequent than hitherto suspected but it can be demonstrated only if the athlete is examined during rest and in the recumbent position It is assumed to be a physiological phenomenon related to heavy physical training

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ST segment isolation and quantification as a means of improving diagnostic accuracy in treadmill stress testing

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Treadmill stress testing and its associated electrocardiographic responses have become firmly established as a method for detection and evaluation of coronary artery disease (CAD)[1-3] While the recent introduction of computer analytic techniques[4-7] has resolved many of the attendant problems of maximal exercise including the high heart rate (with superimposition of P, T and U waves) motion artifact baseline drift and observer variability agreement has not been achieved on optimal diagnostic criteria Much of the latter problem is associated with ST segment responses characterized by J junctional depression but with upward sloping ST segments Moreover diagnostic sensitivity of exercise stress testing remains inadequately low some 25 to 50 per cent of patients with coronary disease remaining undetected by treadmill stress testing [8]

Utilizing a new method of ST segment analysis and computer analytic techniques we have examined these problems and present our results in initial clinical studies These methods are applicable toward improving diagnostic sensitivity and specificity of exercise testing

Methods

Subjects One hundred thirty three patients who underwent treadmill stress testing were divided into three groups as defined below Patients in whom a definite clinical or angiographic diagnosis could not be made were excluded from this study prospectively No cardioactive drugs were being taken during the test digoxin was discontinued at least one week previously

Group I Normal control subjects The 62 subjects comprising this group included 12 normal volunteers and 50 patients who had no evidence of cardiovascular disease Twelve of the 50 patients presented with atypical chest pain but had normal coronary angiograms The average age was 44 years (range 23 to 76) and all group members had normal resting electrocardiograms

Group II Patients with coronary artery disease (CAD) and abnormal stress tests The 29 patients comprising this group averaged 53 years (range 34 to 70) and had unequivocal clinical and/or coronary angiographic evidence of CAD In addition all subjects had a definitely abnormal exercise stress test by standard visual criteria that is 1 mm or greater ST-depression with flat or downsloping ST segments for 0 08 second or longer (defined as "ischemic ST segments)

The patients in Group II were subcategorized (Table I) Subgroup IIA (21 patients) included 11 (38 per cent) having coronary angiograms showing at least 60 per cent obstruction of one or more major coronary arteries or diffuse multivessel disease Ten had previous well-documented acute transmural myocardial infarction with persistent abnormal Q waves (greater than 0 04 second in Leads I II aV_F or V_2 V) on the resting ECG Two patients had combined Q waves and abnormal coronary angiograms

Among Subgroup IIB (eight patients) two had

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Table I Criteria for classifying patients into subgroups A and B

	Group II 29 patients		Group III 42 patients	
Subgroup A	21		31	
Coronary angiograms (only)		(9)		(11)
Transmural myocardial infarction with pathological Qs (only)		(10)		(8)
Combined angiogram and Q		(2)		(12)
Subgroup B	8		11	
Nontransmural myocardial infarction (only)		(0)		(1)
Angina (only)		(6)		(9)
Combined angina and nontransmural myocardial infarction		(2)		(1)

well defined clinical acute myocardial infarction by history having serial cardiac enzyme changes exceeding twice normal and the typical evolutionary pattern These however did not have pathologic Q waves and were considered to have nontransmural infarctions The remaining six patients in this group had a classical history of angina with exertional precordial pain relieved by rest and sublingual nitroglycerin within five minutes In each of these latter cases at least two independent observers concurred that the diagnosis was beyond question

Group III CAD patients with a negative or nondiagnostic exercise test The 42 patients comprising this group had clear evidence of CAD as defined in Group II above The criteria for classifying these patients are shown in Table I, and it is seen that 33 either had coronary angiographic documentation of coronary disease or had a previous well delineated acute myocardial infarction The difference then, between this and Group II is the presence of a normal or nondiagnostic ST segment response during or following exercise stress testing as judged by two independent observers using standard visual criteria i e no ischemic' ST segment changes were evinced The mean age was 51 (range 41 to 74)

It is seen that Subgroups A include only those patients with coronary angiographic documentation of coronary disease and/or clear history of acute transmural myocardial infarction with persistent abnormal Q waves The remaining patients subclassified as B, had historical and enzyme evidence of myocardial infarction without Q waves ('nontransmural' infarctions), or had a typical history of angina This grouping was performed in order to compare those patients with unequivocal evidence of CAD with those presenting with slightly less firm evidence yet still, in our minds the diagnosis being beyond question

Test procedure All subjects were exercised on the same motor driven variable speed/incline treadmill* using the method of Bruce[11] The initial workload was 1 7 m p h at a 10 per cent grade, with both speed and incline being increased every three minutes All patients were encouraged to exercise to their maximum effort unless stopped by the physician monitoring the test Occasionally, increments in speed and grade were made more frequently than at three minutes in order to achieve maximal or near maximal levels of exercise Indications for terminating the tests were appearance of ischemic ST segments visually, moderate or severe chest discomfort regardless of the ECG, severe fatigue preventing the patient from continuing significant arrhythmias or exercise to at least 90 per cent of the age predicted maximal heart rate[12] A minimum exercise heart rate of 130 beats per minute was required for entry into the study

ECG signals were obtained from a single bipolar chest lead which approximated a V_5 Low resistance signal areas were created with proper skin preparation to minimize movement artifact and muscle noise The ECG signal was divided and served as input to two separate recording systems The first was a standard, direct writer electrocardiograph machine† Recordings were made in the sitting and standing positions in the resting state after hyperventilation, and at least twice during each exercise stage Data acquisition continued for at least eight minutes into the recovery period with the patient then sitting From this record, a visual interpretation was made which required agreement by two independent observers This record was utilized for stress test classification of subjects

The second parallel ECG signal served as the input to an ECG preamplifier system‡ with a frequency response of 0 1 to 100 Hz (time constant = 1 12 msec) and a gain ratio of 1,000 1

*Quinton Instrument Co Model 1860 Seattle Wash
†Sanborn Co Model 51 Cambridge Mass
‡Spacelabs, Inc Model 1 0 1600 (Phase II) Chatsworth Calif

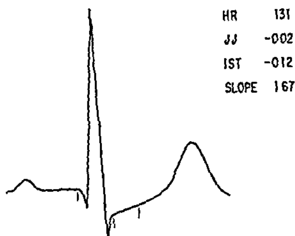


Fig 1 Artist s conception of TV representation of computer a eraged transient (CAT) obtained from one 10-second data period Vertical markers indicate in order baseline J junction and 48 msec along the ST segment After initial selection by the treadmill technician via an interactive computer terminal, markers are automatically set for all subsequent CAT's If temporal alignment changes occur during exercise or recovery new locations can be selected on line real time by adjusting the appropriate marker through the interactive terminal The right portion of the TV display presents the calculated parameters associated with th depicted CAT HR = heart rate JJ = J junction displace ment (mv) IST = isolated ST integral displacement (µv sec) slope = mv /sec rise of the ST segment

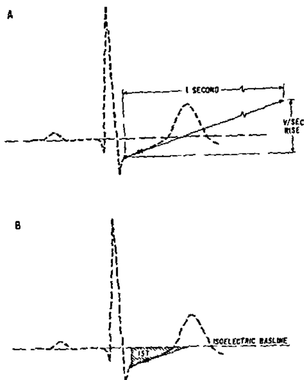


Fig 2 Panel A displays ST segment vector originating at J junction ( ) and passing through 48 msec point of ST segment (x) for determination of slope (rise or fall of ST segment in mv /sec) Panel B shows delineation of isolated ST integral (shaded area) utilizing the same two points i e extrapolating this line automatically to baseline

Interposed line terminating amplifiers were used to suppress common mode noise

Computer sampling The continuous single lead ECG signal was digitalized in 10 second time blocks two to four times per minute by an analog to digital converter under the control of an IBM 1800 MPX computer system Sampling rate was 250 times per second R wave peaks were iden tified within core using pattern recognition tech niques and served as the orientation point for temporal alignment of all acceptable QRS complexes within a given time block. Modifica tion of a previously described method was used for identification of and compensation for base line shift A single QRS complex with elimina tion of accompanying muscle noise and artifact was generated by the method of computer aver aged transients (CAT) R R intervals QRS dura tion polarity and slopes served to identify ectopic complexes which were excluded from analysis.

On line technician-computer interaction The intersection of the P R segment and QRS was taken as baseline No attempt was made to compensate for depressed PR segments or atrial repolarization waves The J point was located at the junction between the QRS and ST segment by the technician utilizing an interactive termi nal and TV representation of the CAT A point 48 msec along the ST segment was then electroni cally identified The choice of 48 msec was partly arbitrary and partly based on an attempt to define an accurate ST-slope without contamina tion from the T wave Atrial repolarization most likely has only a slight influence on the ST voltage at this point[4] Additional adjustments could be made as the exercise test progressed (see Fig 1 for detailed description) In this manner, accurate on line determination of isoelectric base line and ST segment displacement was achieved. J junction and 48 msec ST segment voltages for each generated CAT were logged on line with their respective heart rates sequence markers and patient identification

Table II Group IST integral means (μv sec) for each heart rate span during exercise

Heart rate span	Group I	Group II	Group III
Exercise			
120 129	−0 57	−32 88	−11 16
130 139	−1 93	−51 43	−13 35
140 149	−2 24	−69 81	−10 49
150 159	−2 99	−72 58	−11 77
160 169	−2 72	−140 19	−11 07
170-179	−3 45	−109 17	−17 16
180 189	−2 56		−49 48
Recovery			
180 189	−1 75		−5 21
170 179	−0 85	*	−8 94
160 169	−1 76	−92 72	−5 22
150 159	−0 04	−100 15	−7 33
140-149	−0 24	−69 04	−3 21
130 139	0 07	−23 70	−4 74
120 129	−0 61	−33 95	−7 39
Late recovery			
100 119	−0 31	−26 25	−7 32
80 99	−0 33	−17 43	−5 73

* Insufficient data

Table III Normal IST (μv sec) for each heart rate span as determined from Groups I and II*

Heart rate span	Exercise	Recovery
80 99		−6
100 119		−6
120-129	−6	−4
130 139	−8	−2
140 149	−8	−2
150 159	−10	−2
160 169	−10	−4
170-179	−10	†

*Values with greater negativity are considered abnormal
†Insufficient data

Table IV No (and %) of patients in Groups I and II defined as abnormal according to number of abnormal rate related IST s

Number of rate related IST's	Group I (n = 62)	Group II (n = 29)
1 or more	9 (14 5%)	29 (100%)
2 or more	2 (3 2%)	29 (100%)
3 or more	2 (3 2%)	27 (93 1%)

Isolated ST integral (IST) ST segmental points generated from the CAT pattern recognition program were used to calculate ST segmental slope and the isolated ST integral (IST) ST slope determination as depicted in Fig 2 *A* simply measures the rate of rise or fall (millivolts per second) between J junction and 48 msec Such a technique quantitates rate of change but does not take into consideration the voltage displacement of the ST segment relative to the isoelectric baseline

The *isolated ST integral* (IST) is a function of the magnitude of J junctional displacement and ST segmental slope and serves as a *quantitative measurement* of ST integral displacement from the isoelectric baseline Integral determination is dependent upon the *isolation* of the ST segment from other electrophysiological events This is accomplished by allowing the ST vector starting at the J junction to continue as a straight line *through* the 48 msec point of the ST segment to the isoelectric baseline without interference from T wave forces The IST integral is, therefore bounded by J junction displacement, the sloping ST vector, and the elapsed time along the isoelectric baseline between J junction and the intersection of the ST vector with the baseline (Fig 2, *B*) Such a technique alleviates the problems associated with shortened QT intervals and early onset of the initial T wave limb found during high heart rates In addition, utilization of the IST technique further eliminates the problems inherent in total ' integrative techniques in the presence of inverted or low amplitude T waves (Further details of IST methodology are available in the appendix and on request to the authors)

Development of normal and abnormal criteria of IST All averaged QRST s on an individual subject were evaluated by an IST computation program The evaluation consisted of averaging IST determinations in a given individual at each heart rate span i e , a separate mean IST was calculated for rates between 120 and 129 130 and 139 and so forth Peak heart rate divided exercise and recovery into their respective periods, and the exercise and recovery times were considered separately Each subject s heart rate-related IST s were used to determine normality and abnormality Group IST means for each heart rate span were calculated for exercise recovery and late recovery (rates 80 to 99 100 to 119) and are presented in Table II

Groups I and II were utilized for developing

IST; EXERCISE 120-129

μV-SEC	N1	GROUP I	N2	GROUP II	SPEC	SENS
6.00	1	*	0		0.02	1.00
4.00	3	***	0		0.07	1.00
2.00	4	****	0		0.15	1.00
0.00	7	*******	0		0.28	1.00
-2.00	28	*****************	0		0.80	1.00
-4.00	5	*****	0		0.89	1.00
-6.00	4	****	1	*	0.96	0.96
-8.00	1	*	0		0.98	0.96
-10.00	0		4	****	0.98	0.80
-12.00	0		1	*	0.98	0.76
-14.00	1	*	0		1.00	0.76
-16.00	0		4	****	1.00	0.60
-18.00	0		2	**	1.00	0.52
-20.00	0		1	*	1.00	0.48
-22.00	0		1	*	1.00	0.44
-24.00	0		2	**	1.00	0.36
-26.00	0		0		1.00	0.36
-28.00	0		0		1.00	0.36
-30.00	0		0		1.00	0.36
-32.00	0		0		1.00	0.36
-34.00	0		0		1.00	0.36
-36.00	0		0		1.00	0.36
-38.00	0		0		1.00	0.36
-40.00	0		0		1.00	0.36
-42.00	0		0		1.00	0.36
-44.00	0		3	***	1.00	0.24
-46.00	0		1	*	1.00	0.20
-48.00	0		1	*	1.00	0.16
-50.00	0		0		1.00	0.16
-52.00	0		0		1.00	0.16
-54.00	0		0		1.00	0.16
-56.00	0		0		1.00	0.16
-58.00	0		0		1.00	0.16
-60.00	0		0		1.00	0.16
-62.00	0		0		1.00	0.16
-64.00	0		1	*	1.00	0.12
-66.00	0		0		1.00	0.12
-68.00	0		0		1.00	0.12
-70.00	0		0		1.00	0.12
-72.00	0		0		1.00	0.12
-74.00	0		0		1.00	0.12
-76.00	0		0		1.00	0.12
-78.00	0		0		1.00	0.12
-80.00	0		1	*	1.00	0.08
-82.00	0		0		1.00	0.08
-84.00	0		0		1.00	0.08
-86.00	0		0		1.00	0.08
-88.00	0		1	*	1.00	0.04
-90.00	0		0		1.00	0.04
≥92.00	0		1	*	1.00	0.00

Fig 3 Computer histogram displaying Groups I and II frequency distribution of mean IST integrals (μv-sec) for heart rate span 120 to 129 during exercise Each asterisk represents one subject N1 and N2 are the number of subjects from Groups I and II sampled at this heart rate span In several patients the heart rate quickly jumped from the low hundreds to the 130 s and data for the 120 to 129 span are therefore unavailable The heavy dashed line represents the general area (–6 or –8 μv-sec) where normality can be segregated from abnormality It is at this level that specificity and sensitivity are at their combined highest level 0 96 to 0 98

normal and abnormal criteria All heart rate related mean IST s within these groups were evaluated as to magnitude of IST integral displacement from the isoelectric baseline Normal limits (Table III Fig 3) were then constructed for each of the rate related IST s by selecting a "cut off" value based upon maximal sensitivity and specificity values Thus, normality was determined based upon obtaining *both* sensitivity and specificity as high as possible (between

0 88 and 0 96, respectively, for Groups I and II (Fig 3)] All IST values greater in negativity than the cut off were considered abnormal responses As can be observed in Table III, there is no single normal value for the IST integral, but rather a changing one depending on the heart rate and whether the patient is exercising or in the recovery phase of the test

Individual patient discrimination of normality and abnormality (Group I vs Group II) A single 10 second averaged IST falling outside the defined normal limits is not necessarily diagnostic of coronary ischemia since a variety of artifacts and individual differences may influence an isolated measurement The question, therefore, arose whether one two, or more abnormal" rate related IST s should be required to be present in order to diagnose a patient as having an abnor mal ischemic response Table IV displays the number of patients in Groups I and II which would be diagnosed as being abnormal depending upon whether one, two, or more abnormal IST rate related responses were required Were one to consider a *single* rate related IST to be sufficient for a diagnosis of ischemia false positive re sponders would reach an unacceptable high of 14 5 per cent Occasional appearance of an artifactually depressed ST segment is probably secondary to incomplete elimination of respirato ry and motion noise If, however, two or more rate related IST s are required to fall outside the normal limit before an abnormal patient diagnosis is made, a reasonable false positive level of 3 2 per cent is achieved for the normal group and sensitivity for Group II remains at 100 per cent Specificity shows no improvement when three (or more) abnormal responses are required At this level, sensitivity of Group II falls to 93 1 per cent Therefore, two abnormal rate related IST integrals were selected as the criteria for an ischemic response in a given patient

Definitions (1) Visual ST segment abnormali ty - ischemic ' ST depression (equal to or great er than 1 mm flat or downsloping ST segments for 0 08 second or more) read by the interpreter from the standard ECG tracing (2) IST integral abnormalities - isolated ST segment integral which falls outside the range of normal (3) Rate related IST - normal limits for IST are estab lished for each heart rate bracket, 120 to 129 per minute, 130 to 139 per minute, 140 to 149 per minute etc, both during exercise and in the postexercise recovery period (4) Specificity - number of normal tests/total number of normal patients (5) Sensitivity - number of abnormal tests/total number of abnormal patients (those with coronary artery disease) (6) False positive responses - abnormal tests/total number of nor mal patients (7) False negative responses - nor mal tests/total number of abnormal patients

Results

IST responses

Group I Two (3.2 per cent) of the 62 subjects in this group were detected as being abnormal by IST criteria and are considered false positive responders

Group II All 29 patients in Group II were abnormal IST responders This finding is to be expected, however, as they had clinical CAD and visually abnormal stress tests prior to being included in this group

Group III Seventy nine per cent (33) of the 42 CAD patients in this group were detected as abnormal responders by IST criteria All mem bers of this group originally had normal or nondiagnostic visually interpreted treadmill stress tests Ninety per cent (9 of 10) of those patients classified as having coronary disease on the basis of historical or enzyme evidence of previous nontransmural myocardial infarction or angina (Subgroup IIIB) were found to have IST positive stress tests Seventy five per cent (24 of 32) of Subgroup IIIA—those having abnormal coronary angiograms or history of transmural myocardial infarction with pathologic Q waves—were IST criteria positive

Sensitivity of the IST IST sensitivity was further evaluated by studying the time course of both IST changes and the standard visual abnor malities Group II was selected for this portion of the evaluation since this group contains only CAD patients who developed positive stress tests by visual criteria Fifteen patients (52 per cent) manifested abnormal IST s *before* development of a visually positive test while 17 patients (59 per cent) continued to remain positive *after* disap pearance of a visually abnormal stress test Considering the total abnormal IST responses, 19 per cent (30 of 156) occurred before development of a positive visual test, and 27 per cent (42 of 156) occurred after the positive visual criteria had disappeared Thus the sensitivity of the IST is such that an abnormal response may *precede* the

appearance of a generally accepted ischemic response and may persist for a period of time *after* the cessation of an ischemic ST segment

Discussion

Exercise induced ST segment displacement has been extensively studied and correlated both with presence of known coronary artery disease and the future development of coronary events during follow up periods of up to 20 years [1,2] Most of the early studies employed either the double Masters two step test or submaximal treadmill exercise protocols and have classified patients using merely clinical criteria Coronary angiographic correlation with the double Masters protocol has been far from satisfactory and test sensitivity is reported to range from 35 to 75 per cent when using standard diagnostic criteria[1] false positive responses have been reported to range from 5 to 31 per cent [1] Utilization of maximal or near maximal treadmill stress testing (equal or greater than 85 per cent of age predicted maximum heart rate) has increased sensitivity some 10 to 14 per cent when compared with the former protocol [3] and coronary angiographic correlations with stress test sensitivity range from 60 to 85 per cent [1] [23] False positive responses in the same group of individuals range around 10 to 12 per cent [22] [3,4] Computer analytic techniques have been used in attempting to improve sensitivity and specificity of treadmill testing achieving a sensitivity of 80 to 85 per cent and a specificity of near 90 per cent in one study

Common causes of false negative responses (test insensitivity) include attainment of inadequate heart rate single vessel disease (especially when the right or circumflex coronary artery is involved) use of only a single monitoring lead and appearance of depressed but slowly upsloping ST segments (considered to be in the borderline range of normality abnormality)

The current study was undertaken to improve diagnostic capabilities of treadmill stress testing and has several attributes and unique features (1) The use of computer averaging serves to minimize motion and muscle noise artifact and baseline drift Also operator interaction allows precise on line identification of the ST segment (2) The means of quantifying the amplitude and slope of the ST segment—the IST integral—isolates this segment from the repolarization (T wave) forces (3) Requiring more than one IST to exceed established normal limits before diagnosing an ischemic response minimizes false positive responses (4) Relating IST criteria to a given heart rate has further improved diagnostic capability since ST segment changes normally vary depending upon the level of exercise and its corresponding heart rate (5) Previous studies have looked at the value of computer analysis during exercise testing without regard to whether the test was easily interpretable as being abnormal on the basis of simple inspection [1,9,11] The present study more definitively demonstrates an improved sensitivity utilizing computational analytic techniques (A) by identifying abnormal responders in a group of coronary patients with nondiagnostic exercise tests and (B) by showing a positive or abnormal isolated ST integral both preceding and following visually abnormal (flat or downsloping) ST segments (6) Obviously everyone does not have access to the type of computer assisted techniques utilized here Nevertheless this study had broader reaching conclusions It is clear that upsloping ST segments if sufficiently depressed and/or slowly sloping, may indicate an ischemic response a form of quantification is merely necessary to discriminate normal from abnormal depressions of these upward moving ST segments

No absolute values for total sensitivity and specificity can be determined in this study since a portion of the coronary patients (Group II) were used in criteria development However the results achieved in Group III a group with previously nondiagnostic ST segments appear promising in that a significant yield of abnormalities was evident Further prospective longitudinal studies are needed to determine the role of the isolated ST integral in exercise stress testing

Summary

A new method of ST segment analysis utilizing computer analytic techniques has been employed in treadmill exercise testing with the aim of enhancing diagnostic sensitivity and specificity One hundred thirty three individuals were studied including 62 normal subjects (Group I) 29 patients with coronary disease and clear ischemic ST segment responses to exercise testing (Group II) and 42 patients with coronary disease but normal or nondiagnostic exercise tests (Group

III) The techniques used included computer averaging, to minimize motion artifact and base line drift, a means of isolating the ST segment from the T wave and quantifying ST amplitude and slope (the isolated ST integral, IST), and the relating of the IST to a given heart rate, thus taking cognizance of the dependency of ST depression on heart rate and level of exercise

These methods resulted in a test specificity exceeding 90 per cent and a sensitivity of over 85 per cent Further evidence of the improved sensitivity achieved using these techniques included a 79 per cent (33 of 42) recognition of abnormalities in Group III, patients having normal or nondiagnostic visually interpreted treadmill stress tests (i e no flat or downsloping ST segments of 1 mm or greater) Moreover 15 of 29 patients in Group II (52 per cent) manifested abnormal IST s before development of a typical ischemic ' ST, and in 17 patients (59 per cent), the IST continued to remain positive after disappearance of the characteristic flat or downsloping ST segment

It is concluded that this type of computation analysis adds appreciable diagnostic sensitivity and specificity to treadmill stress testing

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Appendix

Details of computer determination of IST when the ST segment is flat or downsloping can be obtained from the authors In such instances the ST is either extrapolated backward to the baseline—in the case of downward sloping ST—or a constant of 0 015 mv is arbitrarily added to the 48 msec voltage—in the case of flat ST segments—to produce very slight upward sloping

The significance of bundle branch block during acute myocardial infarction

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For over 35 years it has been recognized that the prognosis in acute myocardial infarction is affected adversely by the presence of bundle branch block In addition the fact that the development of bundle branch block may be a precursor of high degree atrioventricular (A V) block is well appreciated[1] Although two recent studies suggest that the association of A V block with bundle branch block in patients with acute myocardial infarction selects a group of patients with an especially high risk of late sudden death the influence of bundle branch block and A V block on short and long term prognosis is still unclear Furthermore the role of temporary and permanent pacemaker therapy remains to be determined This paper reports the experience with bundle branch block in acute myocardial infarction at the Massachusetts General Hospital

Methods and patient series

The records of 876 patients with definite acute myocardial infarction admitted to the Coronary Care Unit were reviewed Of this group 53 had associated bundle branch block—an incidence of 6 per cent An additional 25 patients with acute myocardial infarction and bundle branch block in the hospital s other intensive care areas were identified and included in the series Seven patients had their natural history altered by cardiac surgery during acute hospitalization and therefore were not considered in the overall analysis leaving a group of 71 patients for study

In cases of multiple hospital admissions the first admission in which both an acute myocardial infarction and bundle branch block were present was analyzed.

The electrocardiograms of all patients confined to the Coronary Care Unit were continuously monitored with provision for a 1 minute magnetic tape memory loop Ten second rhythm strips were taken every two hours In addition daily 12 lead electrocardiograms were recorded

The diagnosis of acute myocardial infarction was made by the presence of at least two of the following three criteria

1 A history of pain that was typical of acute myocardial infarction

2 The evolution of Q waves diagnostic of myocardial infarction on the electrocardiogram In patients with left bundle branch block the location of the infarct was known for certain in eight patients in whom an electrocardiogram was recorded acutely before the development of bundle branch block The location was strongly inferred in an additional three patients (two of whom had pathologic confirmation) whose electrocardiograms exhibited striking evolutionary zonal injury changes in the presence of left bundle branch block

3 Abnormal elevation of serum enzymes including glutamic oxaloacetic transaminase creatine phosphokinase and lactic dehydrogenase

Bundle branch block was further characterized

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Table I The relationship of age of conduction defect to location of myocardial infarction*

		New RBBB	*Old RBBB*	*Indet RBBB*	*New LBBB*	*Old LBBB*	*Indet LBBB*
	No hemiblock	4	1	1			
Anterior	LAH	16	5	7	5	2	0
	LPH	2	0	2			
	No hemiblock	1	4	0			
Inf post	LAH	1	1	1	1	1	0
	LPH	0	1	0			
	No Hemi	0	2	0			
Subendo	LAH	0	0	0	1	0	0
	LPH	1	0	0			
	No hemiblock	0	0	0			
Uncertain	LAH	1	0	0	2	4	4
	LPH	0	0	0			

RBBB right bundle branch block LBBB left bundle branch block LAH left anterior hemiblock LPH left posterior hemiblock

as old' if it was known to have been present *prior to the* onset of infarction, new if it was *documented* to occur after the onset of infarction, *and* indeterminate if the precise time of onset could not be identified

Criteria for left anterior hemiblock and left posterior hemiblock in association with right bundle branch block were those described by Rosenbaum and associates [10]

Follow up was obtained by examination of hospital and clinical records communication with the primary physician and direct communication with the patient or an immediate family member

Results

Age and sex of patient Patients ranged in age from 36 to 84 years with a mean age of 63 years There were 50 males and 21 females The duration of right bundle branch block could not be correlated with age However, the 11 patients with old or indeterminate age left bundle branch block were significantly older with an age range of 66 to 84 years and a mean age of 71 years compared to a range of 36 to 83 years and a mean age of 63 years in the other 60 patients ($p < 0.02$)

Location of Infarction The site of infarction in relationship to the various types and time of onset of bundle branch block is shown in Table I

The infarctions were anterior in 45 patients inferior posterior in 11, subendocardial in 4, and of undetermined location in 11

Of the 45 patients with anterior infarctions there were 22 with new right bundle branch block and five with new left bundle branch block while of the 11 patients with inferior posterior infarctions there were only two with new right bundle branch block and one with new left bundle *branch block*

In examining the 26 patients with new right bundle branch block there were 22 with anterior infarctions two with inferior infarctions, one with a subendocardial infarction, and one in whom the location of infarction was uncertain Of the nine patients with new left bundle branch block there were five with anterior and one with inferior infarctions while one was subendocardial and two were of uncertain location

Development of atrioventricular block and mortality Of the entire group of 71 patients, 30 (42 per cent) had second or third degree A V block Of these 30, 19 had sudden onset of complete heart block, one had Mobitz Type I (Wenckebach) progression to complete heart block, nine had Mobitz Type 1 second degree A V block alone and one had Mobitz Type 2 second degree A V block alone Since there was no difference in mortality rates between patients with second degree A V block and those with complete heart block they were grouped together for further analysis In this series the presence of first degree A V block was not a predictive factor for the development of a higher degree of A V block or early or late mortality A V block was transient in all hospital survivors

In the group of 30 patients with second or third degree A V block, there were 17 (57 per cent) hospital deaths In the remaining 13 patients surviving hospitalization there were four late

Table II The relationship of age of conduction defect and presence of A V block to mortality in patients with right bundle branch block

	With A V block			*Without A V block*		
	LAH	*LPH*	*No hemi*	*LAH*	*LPH*	*No hemi*
New RBBB						
No of patients	18	3	1	6	0	4
Hospital deaths	5	2	1	1	0	0
Late deaths (sudden)	2 (2)	1 (1)	0	2 (1)	0	2 (2)
Old RBBB						
No of patients	3	1	0	4	0	7
Hospital deaths	2	1	0	1	0	0
Late deaths (sudden)	1 (1)	0	0	1 (1)	0	0
Indeterminate RBBB						
No of patients	2	0	1	5	2	0
Hospital deaths	1	0	1	1	1	0
Late deaths (sudden)	1	0	0	1	0	0

Table III The relationship of age of conduction defect and presence of A V block to mortality in patients with left bundle branch block

	With A V block			*Without A V block*		
	New LBBB	*Old LBBB*	*Indet. LBBB*	*New LBBB*	*Old LBBB*	*Indet LBBB*
No of patients	5	2	0	4	5	4
Hospital deaths	3	1	0	0	1	0
Late deaths (sudden)	0	0	0	1	4 (4)	3 (3)

deaths (32 per cent) all sudden over a 21 month mean follow up period (range 2 to 57 months) All four occurred in the first year after infarction In the 41 patients without A V block there were five (12 per cent) hospital deaths and 14 (39 per cent) late deaths—10 of which were sudden—among the 36 hospital survivors over a 32 month mean follow up period (range 1 to 173 months) Eight (22 per cent) of these 14 deaths were in the first year and six of these were sudden Thus there was a significantly higher hospital mortality rate in patients with A V block compared to those without ($p < 0.005$) but no significant difference in the incidence of late death among surviving patients with A V block compared to those without ($p > 0.85$)

Table II details the relationship of onset of specific conduction defect to survival in those 51 patients with right bundle branch block Focusing specifically on the 18 patients with new right bundle branch block and left anterior hemiblock 12 (67 per cent) developed A V block and five of these 12 (42 per cent) died in the hospital Of the six patients without A V block there was only one hospital death (N S) There were two late deaths both sudden in the group of seven survivors with A V block and one late sudden death in the group of five without (N S) All three patients with new right bundle branch block and left posterior hemiblock developed A V block — two died in the hospital and the third died suddenly within one week of discharge Of the five patients with new right bundle branch block without associated hemiblock one developed A V block and died in the hospital Two of the remaining four suffered late sudden death All seven patients with old right bundle branch block without associated hemiblock had small infarctions (four of them inferior) with no A V block or mortality

Of nine patients with new left bundle branch block (Table III) five developed A V block and three of these five died in the hospital There were no late deaths among the two survivors Of the four patients without A V block there were no in hospital deaths but one late death These differences did not achieve statistical significance Of the seven patients with old left bundle branch

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	LPH	2	0	2			
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	LAH	1	1	1	1	1	0
	LPH	0	1	0			
Subendo	No Hemi	0	2	0			
	LAH	0	0	0	1	0	0
	LPH	1	0	0			
Uncertain	No hemiblock	0	0	0			
	LAH	1	0	0	2	4	4
	LPH	0	0	0			

RBBB right bundle branch block LBBB left bundle branch block LAH left anterior hemiblock LPH left posterior hemiblock

as 'old' if it was known to have been present prior to the onset of infarction, 'new' if it was documented to occur after the onset of infarction, and 'indeterminate' if the precise time of onset could not be identified

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In the group of 30 patients with second or third degree A V block there were 17 (57 per cent) hospital deaths In the remaining 13 patients surviving hospitalization there were four late

These patients were significantly older than the remainder of the group and their high late mortality may reflect the fact that their left bundle branch block was associated with advanced myocardial disease which antedated the infarction

There has been no study in which the use of temporary pacemakers has been shown to statistically alter survival when myocardial infarction is accompanied by the development of bundle branch block despite the extraordinarily high incidence of A V block in such patients Some authors have suggested that prophylactic pacemakers are not warranted because of associated complications and the lack of proved effectiveness. The data in this paper do not help to settle this controversy However the presence of a prophylactic temporary standby pacemaker made the onset of complete heart block a hemodynamically smooth and clinically undetectable event in several patients obviating the necessity for pacemaker placement under emergency conditions It is our current policy to use temporary *prophylactic* pacemakers in all patients with acute myocardial infarction and left bundle branch block or right bundle branch block and associated hemiblock which is new or of indeterminate onset Stability of the electrode tip is usually assured when the *electrode is inserted* through the external or internal jugular or subclavian veins

Several authors have noted an extraordinarily high incidence of late sudden death in patients with acute myocardial *infarction and bundle* branch block who developed transient A V block and were subsequently discharged from the hospital with normal A V conduction [8,9] Two of these papers documented a dramatic reduction in late sudden death with the institution of permanent demand right ventricular pacing When the data from these two papers are pooled a high degree of statistical significance is achieved ($p < .01$) but the total number of patients was only 25 Three patients in our study group were discharged with permanent pacemakers but one died suddenly during the first year after infarction

Although current indirect evidence gives weight to sudden complete heart block as a major cause of *late sudden* death in patients with acute myocardial infarction bundle branch block and transient complete A V block the exact mechanism of death still remains uncertain If the cause is asystole then obviously a pacemaker may be lifesaving However if patients die from ventricular fibrillation a pacemaker would probably be of no value in preventing late sudden demise Indeed one of our three patients with a functioning pacemaker died suddenly Before we may unequivocally recommend prophylactic pacemakers which in themselves carry a morbidity as well as a substantial expense more data are needed Either a randomized study of the use of permanent prophylactic pacemakers in a large group of patients or pooled data from several centers would appear indicated

Summary

Analysis of the course of 71 patients with acute myocardial infarction complicated by bundle branch block (BBB) confirms a high incidence of atrioventricular (A V) block (42 per cent) and severe pump failure (35 per cent) in these patients Hospital mortality was not correlated with BBB per se but rather with the associated development of second or third degree A V block (57 per cent with A V block vs 12 per cent *without A V block* $p < .0005$) or severe pump failure (35 per cent with vs 11 per cent without severe pump failure $p < .001$) However late *mortality* was high and not significantly different among those surviving hospitalization whether transient A V block was present or absent Eight of 11 late deaths were sudden Temporary pacing could not be shown to alter hospital survival statistically but made the onset of complete heart block a hemodynamically smooth and clinically undetectable event in several patients who later survived The place of permanent pacing in these patients cannot be clearly determined on the basis of this study or in the available literature More data obtained either by pooling the experience of several centers or from a prospective randomized study are needed to determine the indications for permanent pacemakers

The authors thank Mrs Lee Roberts and Miss Barbara Noel for their technical assistance Mr Edward Kaplan and Mr John Newell for statistical analysis and Miss Stephanie Murray for her secretarial assistance

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block, two developed A-V block and one died in the hospital. In the five patients without A-V block, there was one hospital and four late deaths.

Development of pump failure and mortality: Severe pump failure as manifested by pulmonary edema or cardiogenic shock was present in 25 of the 71 patients (35 per cent). An additional 14 patients were judged to have mild to moderate left ventricular failure clinically or radiographically. Sixteen of the 25 patients with severe pump failure (64 per cent) and three of the 14 patients with mild to moderate left ventricular failure (21 per cent) died during the initial hospitalization compared to only two hospital deaths in the 32 patients without pump failure (6 per cent). Hospital mortality was significantly greater in the group with severe pump failure when compared to the other two groups ($p < .001$).

In the group of 18 patients with new right bundle branch block and left anterior hemiblock, six patients had cardiogenic shock and two had pulmonary edema with four hospital deaths compared to one hospital death in the six patients with mild to moderate left ventricular failure and one hospital death in the group of without pump failure.

Two of three patients with new right bundle branch block and left posterior hemiblock had cardiogenic shock and died in the hospital.

Of the nine patients with new left bundle branch block, two developed cardiogenic shock and died in the hospital, three developed mild to moderate left ventricular failure, one of whom died in the hospital and four had no pump failure and no mortality.

Experience with Pacemakers: The impact of pacemaker therapy on mortality was difficult to ascertain. Temporary right ventricular pacemakers were placed in 37 of the 71 patients. Pacing was required in 15 of these 37 patients. Of these 15, the pacemaker was placed after the need arose in 10 patients and six of them died. Of the five patients in whom the pacemaker was placed prophylactically, two died. Although there was no statistical difference in these two groups of patients, it was judged that (1) in at least two patients the presence of a prophylactic temporary pacemaker made the onset of complete heart block a hemodynamically smooth and clinically undetectable event, and (2) the fortuitous presence of trained personnel capable of placing an emergency right ventricular pacemaker was life saving in at least one patient who developed complete heart block without the benefit of a prophylactic pacemaker in place. There were no serious complications associated with the use of temporary pacemakers.

Only three patients received permanent pacemakers. All had complete heart block with subsequent recovery of normal A-V conduction. One had new left bundle branch block and two had new right bundle branch block with left anterior hemiblock. Two are alive at 15 and 16 months but one patient died suddenly eight months after infarction. Although a postmortem examination was not performed, the pacemaker appeared to have been functioning normally at the time of death.

Discussion

This study demonstrates that when acute myocardial infarction is accompanied by bundle branch block and especially when this conduction defect is a result of the infarction, there is a very high incidence of A-V block and pump failure. Hospital mortality in this patient population was not correlated with the presence of bundle branch block per se as in other studies[7,8,11,1] but rather with the associated development of A-V block or pump failure. The hospital mortality in those patients in this study who did not develop A-V block was only 12 per cent and in those who did not manifest severe pump failure, it was 11 per cent.

By analyzing the time of development of bundle branch block in relation to the onset of myocardial infarction we were able to determine that patients with left bundle branch block or new right bundle branch block and associated hemiblock had the highest incidence of A-V block.

Although there was a slightly higher incidence of late death during the first year after infarction in those hospital survivors who developed A-V block compared to those who did not (32 per cent vs 22 per cent), this difference did not achieve statistical significance. Furthermore, over the entire course of the study, late mortality was comparable in these two groups (32 per cent vs 39 per cent).

There was a group of patients with an unusually high late mortality—namely those with old or indeterminate age left bundle branch block

Influence of variations in blood flow on renal A-V oxygen difference and renal oxygen consumption in heart failure. A clinical study

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Renal function studies in chronic heart disease[2] have demonstrated reduction of the renal blood flow and to a lesser extent a fall of the glomerular filtration rate. These changes might occur before systemic hemodynamic alterations are found and before congestive heart failure has appeared. Few data dealing with the relationship between renal hemodynamic and renal oxygen extraction in heart diseases are available. In the present investigation the relationships between renal hemodynamic alteration and renal oxygen extraction in a series of patients representing a spectrum of severity of heart insufficiency have been studied. The results of simultaneously determined renal sodium reabsorption are also presented.

Material and methods

A total of 18 patients all suffering from rheumatic heart disease involving the mitral valve were selected for the present study. There were six men and 12 women, all of them of middle age. Hemodynamically the patients presented a wide spectrum of heart failure (N.Y.H.A. Class II to IV). Their cardiac output measured in connection with right heart catheterization (Fick's method) varied between 1.7 and 6.0 L. per minute with a mean value of 3.39 L. per minute. All patients had been treated with diuretics for several months prior to admission and this treatment was discontinued at the time of study.

None of the patients were suspected of renal disease and the functional changes found were in our opinion solely due to the systemic hemodynamic changes.

Right renal vein catheterization was performed in all cases. Satisfactory positioning of the catheter tip in the renal vein was verified by injection of a small amount of radiographic contrast material and by oximetry of renal vein and inferior vena caval blood samples demonstrating high oxygen saturation in the former. The results of para-amino-hippurate (PAH) extraction also confirmed the position of the catheter. Renal A-V oxygen difference was determined as the difference between oxygen content in blood drawn simultaneously from the catheter in the right renal vein and from an indwelling polyethylene catheter placed percutaneously in the femoral artery. The oxygen content was calculated from the hemoglobin concentration and the hemoglobin oxygen saturation spectrophotometrically determined. The range for normal renal A-V oxygen difference was taken from 10.9 to 18.7 ml. per liter.[3]

The clearance of PAH (C_{PAH}) was studied with a contrast infusion technique according to the method described by Brodwall and Laake.[4] Renal plasma flow (RPF) was calculated from C_{PAH} and renal extraction ratio of PAH (E_{PAH}). Renal blood flow (RBF) was calculated from RPF and hematocrit.

Renal oxygen consumption was derived as the product of renal blood flow and renal A-V oxygen difference, the results expressed as millimoles per minute. This figure was compared with a mean value of 0.70 mM per minute estimated from a series of normals examined by Brodwall and Laake[4] using the same methods as in the present study.

Urine specimens were obtained from an

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Table I Renal oxygen consumption and renal blood flow in cardiac patients with normal renal A V oxygen difference compared with the same values in patients with abnormally increased renal A V oxygen difference (mean ± 1 S D)

	Renal A V oxygen difference		
	Normal (n = 8)	*Increased (n = 10)*	*t test*
Renal oxygen consumption (mmol /min)	0.33 ± 0 09	0 49 ± 0 12	0 01 > p > 0 001
Renal blood flow (ml / min.)	619 9 ± 141 1	4?6 2 ± 167 3	0 05 > p > 0 01

Table II Renal oxygen consumption and net sodium reabsorption in cardiac patients with normal renal A V oxygen difference compared with the same data in patients with abnormally increased renal A V oxygen difference (mean ± 1 S D) All figures have been corrected to a standard surface area of 1 73 M²

	Renal A V oxygen difference		
	Normal (n = 8)	*Increased (n = 8)*	*t test*
Renal oxygen cons. (mmol./ min./1 73 M)	0.3? ± 0 07	0 51 ± 0 14	0 01 > p > 0 001
Net sodium reab (mmol./ min./1 73 M)	11.5 ± 3 0	11.3 ± 3 9	p > 0 05

normal conditions approximately 25 per cent of the cardiac output flows through the kidneys

Renal A V oxygen difference and renal blood flow The renal A V oxygen difference varied between 4 7 and 40 7 ml per liter with a mean value of 20.55 ml. per liter Values higher than normal were found in 10 out of 18 patients studied In Fig 3 the values for renal A V oxygen difference are plotted against the corresponding values for renal blood flow With a few exceptions renal A V oxygen difference varied within normal range in all patients whose renal blood flow was higher than 400 to 500 ml per

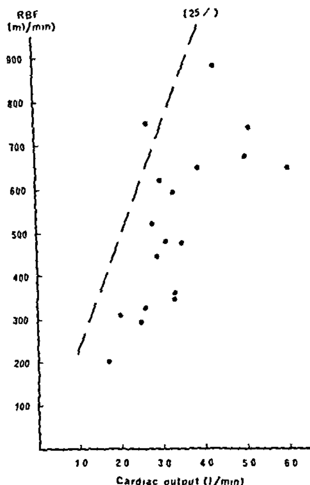


Fig 2 Relationship between renal blood flow and cardiac output The interrupted line indicates the percentage of the cardiac output perfusing the kidneys if a normal distribution of cardiac output persisted

minute—at lower values for renal blood flow the A V oxygen differences in all cases were higher than normal

Renal oxygen consumption and sodium reabsorption Renal oxygen consumption varied between 0 13 and 0 67 mM per minute with a mean value of 0 419 mM per minute The mean renal oxygen uptake corresponded to 60 per cent of the predicted normal metabolic rate and ranged between 19 and 96 per cent Patients with abnormally great renal A V oxygen difference had significantly higher renal oxygen consumption than patients with normal renal A V oxygen difference The discrepancy in this respect between the renal metabolic rate in patients with increased vs those with normal renal A V oxygen difference is shown in Table I

We measured tubular sodium reabsorption as a

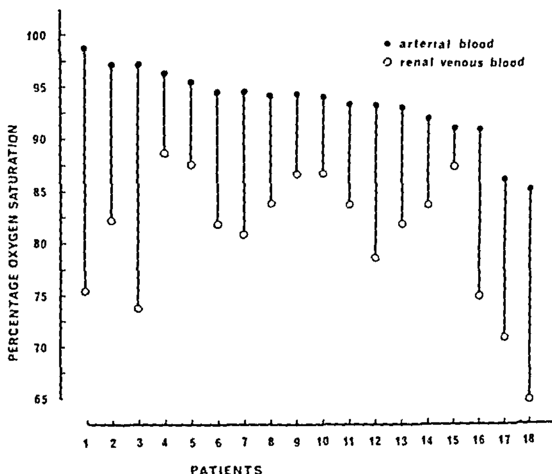


Fig 1 Comparison between the oxygen contents of arterial ( ) and renal vein (o) blood in 18 cardiac patients

indwelling urethral catheter The bladder was emptied by suprapubic pressure and rinsed with saline solution after each collecting period The amount of sodium reabsorbed in the tubulus was calculated as the difference between the amount of sodium filtered and the amount of sodium excreted Serum sodium was measured with an Auto Analyzer and sodium concentration in urine was determined by flame photometry

Statistical significance of differences between means was calculated with Student s t test Regression lines were drawn according to equations found by the method of least squares Coefficients of correlation were calculated as described by Snedecor [6] P values higher than 0 05 were not considered significant

Results

Arterial and renal venous blood oxygen saturation The relationships between arterial and renal venous blood oxygen saturation are shown in Fig 1 The arterial oxygen saturation was within the normal range of 92 to 95 per cent except in two patients (cases 17 and 18) The latter two patients demonstrated a slight arterial hypoxemia The renal venous blood oxygen saturation varied within the range of 65 to 88 per cent Thus while the arterial samples showed only minor variations in oxygen saturation, samples from the renal vein obtained at the same time showed large interindividual differences The low saturation of renal vein blood seen in many of the patients studied is due to an increased renal extraction and not to an incomplete arterial blood saturation On the other hand, arterial hypoxemia apparently has not affected the ability of the kidney to increase its oxygen extraction as seen in a few cases

Cardiac output and renal blood flow The cardiac output varied between 1 7 and 6 0 L per minute, with a mean value of 3 39 L per minute The corresponding range for renal blood flow was 200 and 870 ml per minute with a mean value of 512 1 ml per minute Thus the kidneys received on an average 15 per cent of the cardiac output Fig 2 shows a correlation plot between the renal blood flow and cardiac output illustrating that the changes in these parameters parallel one another The diagram also shows that in all patients with one exception, the diminution in renal blood flow is relatively larger than the fall in cardiac output, if one estimates that under

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Net sodium reab (mmol./ min /1 73 M.)	11.5 ± 3 0	11.3 ± 3 9	p > 0 05

normal conditions approximately 25 per cent of the cardiac output flows through the kidneys

Renal A V oxygen difference and renal blood flow The renal A V oxygen difference varied between 4 7 and 40 7 ml per liter with a mean value of 20 55 ml per liter Values higher than normal were found in 10 out of 18 patients studied In Fig 3 the values for renal A V oxygen difference are plotted against the corresponding values for renal blood flow With a few exceptions renal A V oxygen difference varied within normal range in all patients whose renal blood flow was higher than 400 to 500 ml. per

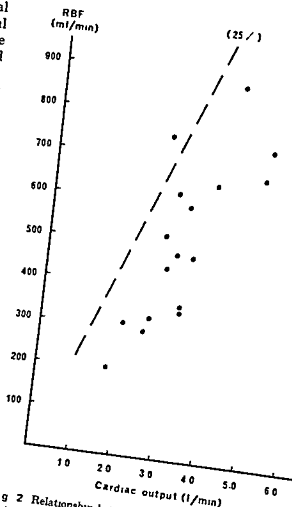


Fig 2 Relationship between renal blood flow and cardiac output The interrupted line indicates the percentage of the cardiac output perfusing the kidneys if a normal distribution of cardiac output persisted

minute—at lower values for renal blood flow the A V oxygen differences in all cases were higher than normal

Renal oxygen consumption and sodium reabsorption Renal oxygen consumption varied between 0 13 and 0 67 mM per minute with a mean value of 0 419 mM per minute The mean renal oxygen uptake corresponded to 60 per cent of the predicted normal metabolic rate and ranged between 19 and 96 per cent Patients with abnormally great renal A V oxygen difference had significantly higher renal oxygen consumption than patients with normal renal A V oxygen difference The discrepancy in this respect between the renal metabolic rate in patients with increased vs those with normal renal A V oxygen difference is shown in Table I

We measured tubular sodium reabsorption as a

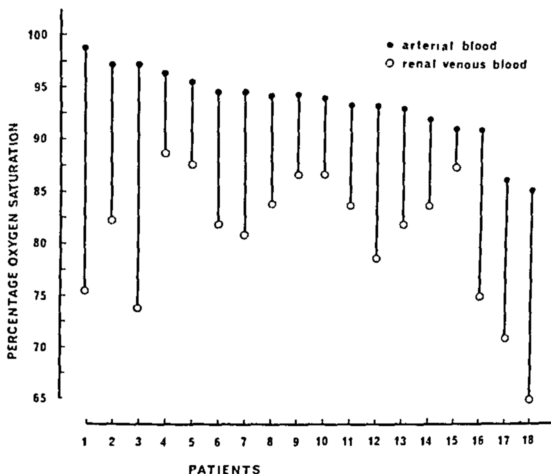


Fig 1 Comparison between the oxygen contents of arterial ( ) and renal vein (o) blood in 18 cardiac patients.

indwelling urethral catheter The bladder was emptied by suprapubic pressure and rinsed with saline solution after each collecting period The amount of sodium reabsorbed in the tubulus was calculated as the difference between the amount of sodium filtered and the amount of sodium excreted Serum sodium was measured with an Auto Analyzer and sodium concentration in urine was determined by flame photometry

Statistical significance of differences between means was calculated with Student s t test Regression lines were drawn according to equations found by the method of least squares Coefficients of correlation were calculated as described by Snedecor [6] P values higher than 0 05 were not considered significant

Results

Arterial and renal venous blood oxygen saturation The relationships between arterial and renal venous blood oxygen saturation are shown in Fig 1 The arterial oxygen saturation was within the normal range of 92 to 95 per cent except in two patients (cases 17 and 18) The latter two patients demonstrated a slight arterial hypoxemia The renal venous blood oxygen saturation varied within the range of 65 to 88 per cent Thus while the arterial samples showed only minor variations in oxygen saturation, samples from the renal vein obtained at the same time showed large interindividual differences The low saturation of renal vein blood seen in many of the patients studied is due to an increased renal extraction and not to an incomplete arterial blood saturation On the other hand arterial hypoxemia apparently has not affected the ability of the kidney to increase its oxygen extraction as seen in a few cases

Cardiac output and renal blood flow The cardiac output varied between 1 7 and 6 0 L per minute, with a mean value of 3 39 L per minute The corresponding range for renal blood flow was 200 and 870 ml per minute with a mean value of 512 1 ml per minute Thus the kidneys received on an average 15 per cent of the cardiac output Fig 2 shows a correlation plot between the renal blood flow and cardiac output illustrating that the changes in these parameters parallel one another The diagram also shows that in all patients, with one exception the diminution in renal blood flow is relatively larger than the fall in cardiac output if one estimates that under

Table I Renal oxygen consumption and renal blood flow in cardiac patients with normal renal A V oxygen difference compared with the same values in patients with abnormally increased renal A V oxygen difference (mean ± 1 S D)

	Renal A V oxygen difference		
	Normal (n = 8)	*Increased (n = 10)*	*t test*
Renal oxygen consumption (mmol /min)	0.33± 0 09	0 49± 0 12	0 01>p>0 001
Renal blood flow (mL/ min.)	619 9 ±141 1	426.2 ±167.3	0 05> p >0 01

Table II Renal oxygen consumption and net sodium reabsorption in cardiac patients with normal renal A V oxygen difference compared with the same data in patients with abnormally increased renal A V oxygen difference (mean ± 1 S D) All figures have been corrected to a standard surface area of 1 73 M ²

	Renal A V oxygen difference		
	Normal (n = 8)	*Increased (n = 8)*	*t test*
Renal oxygen cons (mmol / min /1 73 M.)	0 32 ± 0 07	0 51 ± 0 14	0 01>p>0 001
Net sodium reab (mmoL/ min /1 73 M)	11.5 ± 3 0	11 3 ± 3 9	p > 0 05

normal conditions approximately 25 per cent of the cardiac output flows through the kidneys

Renal A V oxygen difference and renal blood flow The renal A V oxygen difference varied between 4 7 and 40 7 ml per liter with a mean value of 20 55 ml per liter Values higher than normal were found in 10 out of 18 patients studied In Fig 3 the values for renal A V oxygen difference are plotted against the corresponding values for renal blood flow With a few exceptions renal A V oxygen difference varied within normal range in all patients whose renal blood flow was higher than 400 to 500 ml per

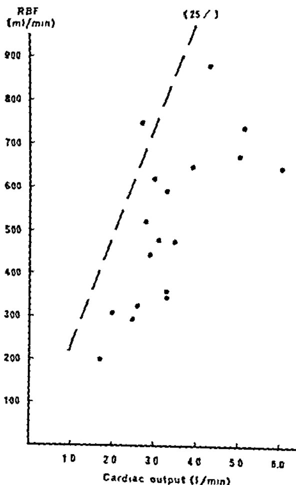


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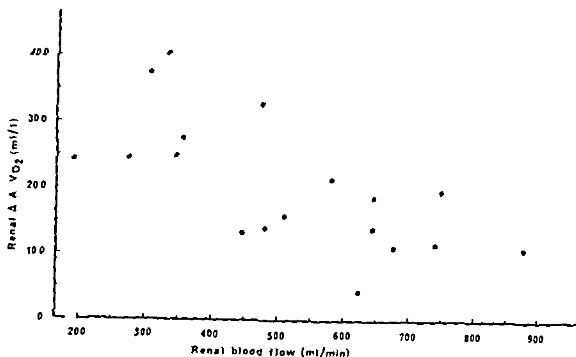


Fig 3 Renal A V oxygen difference and renal blood flow Shaded area marks normal range for renal A V oxygen difference previously reported by Cargill and Hickam [3]

difference between the amount of sodium filtered and the amount of sodium excreted Due to sampling errors data are lacking for two patients Fig 4 shows the relationship between the oxygen consumption and sodium reabsorption A large scatter was found and both small and large amounts of sodium reabsorption occur with high and low renal metabolic rates The slope of the regression line relating renal oxygen consumption and sodium reabsorption was not significantly different from zero Table II gives a direct comparison between data for oxygen consumption and sodium reabsorption in patients with normal A V oxygen difference and those with an increased A V oxygen difference The amounts of sodium reabsorbed were nearly identical while the intergroup difference in oxygen consumption was significant

Discussion

The aim of the circulation to any organ is to provide the optimal physiological environment for the cells under a wide variety of conditions Oxygen transport is the product of systemic or regional blood flow and the arterial oxygen content, and is related to the oxygen consumption by the oxygen extraction ratio

The kidney is an organ normally characterized by a high blood flow To satisfy the oxygen demand of the kidneys under normal conditions only a comparatively low extraction ratio of oxygen is necessary The normal kidney has a high renal oxygen consumption in relation to the weight of the organ [3]

In patients with essential hypertension, Cargill and Hickam[3] observed that both flow and oxygen consumption were decreased, probably due to lowered metabolic demands Merrill[1] found that the decreased renal blood flow accompanying congestive heart failure was compensated by an increased oxygen extraction so that oxygen consumption remained normal Our data depict a somewhat different pattern of flow-oxygen consumption relationship In our patients with mitral valve disease we found that renal A V oxygen difference was small and remained within the normal range despite an advanced reduction of renal blood flow Abnormal large A V oxygen differences with increased extraction of oxygen were with a few exceptions limited to those patients whose renal blood flow had fallen to 400 to 500 ml per minute or less indicating a severe reduction in blood supply The renal oxygen consumption was generally reduced compared with normal subjects but tended to increase when A V oxygen difference increased

The present studies thus show that kidneys in heart failure apparently behave in a manner which contrasts with the rest of the body As cardiac output decreases, total body oxygen consumption initially is maintained by increased oxygen extraction With severe reduction in

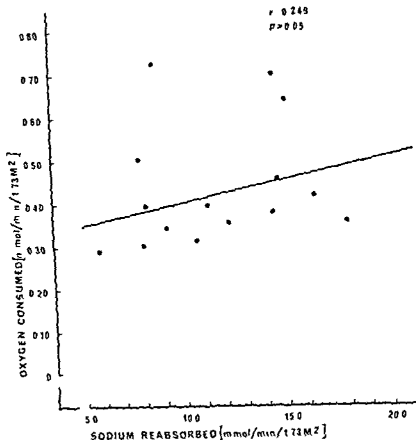


Fig 4 Correlation plot between net sodium reabsorption and renal oxygen consumption All figures have been corrected to a standard surface area of 1 73 M

cardiac output oxygen consumption has been found reduced as an adjustment to the critically reduced oxygen delivery to the tissue[7]

There is no readily apparent explanation for the various renal metabolic patterns in heart failure demonstrated in the present study One possibility considered was that the kidney might behave in a sense of a flow limited tissue as suggested by Pappenheimer and Kinter[4] Although the oxygen consumption was decreased at moderately reduced renal blood flow levels the present study demonstrated that drastically reduced flow values were associated with increased oxygen extraction and virtually increased oxygen consumption The renal oxygen uptake was therefore not a function of the renal blood flow *per se* This finding is in accordance with previous experimental studies A second explanation was that the kidney might be unable to increase oxygen extraction from the blood when flow is reduced Again the marked increase in oxygen extraction seen when flow is minimal makes this hypothesis untenable Third as several studies[9,1] have demonstrated a linear correlation between sodium transport and oxygen consumption it was tempting to conclude that the variations in oxygen requirements were due to variations in active sodium transport However contrary to expectations the present study failed to demonstrate any relationship between sodium reabsorption and oxygen consumption At the same metabolic rate a wide range of sodium was transported These findings are commented upon more closely in a paper to be published and are in accordance with experimental data in dogs showing a rather constant renal metabolic rate over a wide range of tubular sodium reabsorption and that the net sodium reabsorption may be regulated by variations in passive transport in the proximal tubules[3]

Another explanation for our findings seems to be that at moderately reduced flow rates the kidneys either suffer curtailment of oxidative metabolism or adopt their function to reduced

oxygen demand Our results could indicate a shift to a more aerobic renal metabolism in advanced heart failure with minimal renal blood flow In a recently published study Trimble and Bowman[14] emphasized that both glucose and endogenous fatty acids are required for maximal renal sodium reabsorption It is also possible that the substrate requirements for transport of sodium may change in different circulatory situations and on account of such substrate changes variations in the oxygen demand for the metabolism might occur Furthermore Sparks and co workers[15] have demonstrated that at low renal blood flow in experimental chronic heart failure a redistribution of the flow within the kidney occurred Outer cortical blood flow was reduced, inner cortical and outer medullary flow was increased During the renal circulatory derangement, sodium reabsorption was increased suggesting a causal relationship between sodium retention and intrarenal distribution of blood flow

Summary

In the present study renal A V oxygen difference and renal blood flow were measured in 18 patients with mitral valvular disease The renal sodium reabsorption and oxygen consumption have also been measured

The renal A V oxygen difference was small and remained within the normal range despite large reductions in renal blood flow Only when flow fell to between 400 and 500 ml per minute there was a rise in A V oxygen difference The renal oxygen consumption was in general reduced compared with normal subjects but tended to increase in those patients who also had the greatest values for A V oxygen difference The renal oxygen consumption was found to vary independently of the sodium reabsorption

Our results indicate a shift to a more aerobic renal metabolism in advanced heart failure when renal blood flow is drastically reduced It is possible that the variations in oxygen demand may reflect changes in substrate requirements for transport of sodium in different circulatory situations Redistribution of flow within the kidney at low renal blood flow as well as the possibility of passive transport of sodium in the proximal tubules might also account for the changing relationship between A V difference and renal blood flow

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Correlation of abnormal Q waves, coronary pathology, and ventricular contractility

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Pardee was the first to call attention to the large Q wave in Lead III in patients with angina pectoris and to document the electrocardiographic signs of acute myocardial infarction Levine was also aware of the Q wave as a diagnostic sign in coronary artery disease Fenichel and Kugell extended these initial observations by pathologic correlations and noted that a large Q wave in Lead III is probably due to involvement of the septum particularly in its posterior portion Since these early studies the Q wave has become firmly established as an important diagnostic sign of transmural myocardial infarction Horan and associates performed the largest electrocardiographic and pathologic correlation to date They found that Q waves of 0 03 second duration had an over all accuracy of 79 per cent With the advent of cineangiographic methods for evaluation of both coronary artery anatomy and ventricular contractility an important diagnostic tool was added Although the ventriculogram has received some emphasis most investigations have concentrated on the correlation of coronary pathology and the electrocardiogram However the electrocardiogram is a reflection of depolarization and repolarization of the myocardium and relates to coronary pathology only insofar as that pathology results in myocardial injury Coronary occlusive lesions may or may not result in myocardial injury depending upon the degree of occlusion adequacy of collateral circulation and myocardial oxygen requirement Therefore, the present study was undertaken to determine whether the Q wave of the clinical electrocardiogram correlates better with ventricular contractility or with coronary pathology as evaluated by cine coronary arteriography

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Material and methods

Electrocardiographic and angiographic findings were reviewed in all adult patients undergoing cardiac catheterization from Jan 1 1970 to Dec 31 1972 at Thomas Jefferson University Hospital Four hundred and ninety two patients who had coronary artery disease and good quality electrocardiograms and left ventriculograms were included

A Q wave was considered to be significant if it was 0 04 second or greater in width Tall R waves in Leads V or V_2 were defined as those equal to or greater than the S waves in the same leads These latter findings were used as criteria for true posterior myocardial infarction

Cine coronary arteriography was performed by means of the Sones technique [°] with meglumine diatrizoate and sodium diatrizoate 76 per cent A General Electric image intensifier and 35 mm film were used Film speed was 60 frames per second A 6 inch image intensifier tube was employed for magnification Left ventriculograms were obtained in the right anterior oblique projection with the use of the same equipment contrast and film speed A 9 inch image intensifier tube was used for ventriculography The volume of contrast material ranged from 25 to 40 c c per injection

Critical coronary arteriographic lesions were

Table I Inferior wall

Leads with significant Q	No of patients	Ventriculographic contractile pattern				Coronary pathology ≥ 75 per cent occlusion in dominant or balanced circulation
		H	A	D	N	
II	0	–	–	–	–	–
III	53	7 (13%)	11 (21%)	5 (9%)	30 (57%)	36 (68%)
aVF	2	0 (0%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)
II III	1	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
II aVF	0	–	–	–	–	–
III aVF	49	12 (24%)	20 (41%)	2 (4%)	15 (31%)	36 (73%)
II III aVF	47	14 (30%)	25 (53%)	2 (4%)	6 (13%)	36 (77%)

H = hypokinesis A = akinesis D = dyskinesis N = normal

Table II Anterior wall

Leads with significant Q	No of patients	Ventriculographic contractile pattern				Coronary pathology ≥ 75% occlusion in LAD artery
		H	A	D	N	
V	8	2 (25%)	1 (12%)	1 (12%)	4 (51%)	6 (75%)
V	15	6 (40%)	4 (27%)	2 (13%)	3 (20%)	9 (60%)
V and/or V V	21	5 (24%)	7 (33%)	4 (19%)	5 (24%)	18 (86%)
Any two leads (V)	20	2 (10%)	6 (30%)	6 (30%)	6 (30%)	16 (80%)

H = hypokinesis A = akinesis D = dyskinesis N = normal LAD = left anterior descending

Table III Apex

Leads with significant Q	No of patients	Ventriculographic contractile pattern				Coronary pathology ≥ 75% occlusion in LAD artery
		H	A	D	N	
V	8	1 (12%)	1 (12%)	4 (50%)	2 (26%)	6 (75%)
V	15	6 (40%)	3 (20%)	3 (20%)	3 (20%)	9 (60%)
V and/or V V_4	21	1 (5%)	7 (33%)	9 (43%)	4 (19%)	18 (86%)
Any two leads (V)	20	1 (5%)	9 (45%)	8 (40%)	2 (10%)	16 (80%)

H = hypokinesis A = akinesis D = dyskinesis N = normal LAD = left anterior descending

defined as being equal to or greater than 75 per cent obstruction of the vessel lumen Coronary arterial dominance referred to the vessel supplying the posterior descending coronary artery to the inferior surface of the heart When a branch from both the right and left circumflex coronary arteries contributed to inferior wall supply, the circulation was referred to as balanced

The criteria of Herman and associates[11] were used to describe localized areas of abnormal myocardial contraction Hypokinesis was defined as diminished myocardial contractility Akinesis was used to describe an absence of myocardial motion and dyskinesis referred to parodoxical motion during systole All data were analyzed in a double blind fashion

Results

The results are summarized in Tables I through V In Table I, Q waves in Leads II, III and aV_F, and combinations thereof are matched with abnormalities in inferior wall contractility and critical coronary occlusion (≧ 75 per cent) of the coronary artery supplying the inferior wall Table II correlates Q waves in the precordial leads with ventriculographic features of the anterior wall and critical occlusion of the left anterior descending coronary artery Table III correlates Q waves

Table IV Relatively tall R waves with upright T waves in Leads V_{1-2}

No of patients	RTR V_1	RTR V_2	*Ventriculographic contractile pattern of posterior portion of inferior wall*				*Coronary pathology ≥ 75 per cent occlusion in dominant or balanced circulation*
			H	*A*	*D*	*N*	
9	9 (100%)	1 (11%)	1 (11%)	4 (44%)	0	4 (44%)	5 (55%)

H = hypokinesis A = akinesis D = dyskinesis N = normal

Table V Normal electrocardiograms

No of patients	*Ventriculographic contractile pattern*				*Coronary pathology ≥ 75 per cent occlusion*
	H	*A*	*D*	*N*	
Inferior wall 269	39 (14%)	16 (6%)	5 (2%)	209 (78%)	In dominant vessel 127 (47%)
Anterior wall 269	42 (16%)	10 (4%)	17 (6%)	200 (74%)	In LAD coronary artery 131 (49%)
Apex 269	27 (10%)	18 (7%)	33 (12%)	191 (71%)	In LAD coronary artery 131 (49%)

H = hypokinesis A = akinesis D = dyskinesis N = normal LAD = left anterior descending

in the precordial leads with ventriculographic features of the ventricular apex and critical occlusion of the left anterior descending coronary artery Table IV correlates the finding of relatively tall R (RTR) waves in Lead V_1 or Lead V_2 with ventriculographic features of the posterior part of the inferior wall and occlusion of the dominant vessel or the right or circumflex coronary artery if the circulation was balanced Table V correlates ventriculographic and arteriographic data on 269 patients with coronary artery disease but without significant Q waves

Discussion

Beginning with the work of Pardee and Fenichel the pathologic Q wave has come to be regarded as the prime indicator of transmural myocardial infarction It is of importance therefore to establish the statistical correlation between pathologic Q waves and ventriculographic correlates of myocardial infarction Horan and associates correlated pathologic Q waves with the findings in a very large number of carefully performed postmortem examinations Interest is increasing however in evaluating patients for possible coronary artery bypass surgery and many patients are undergoing coronary angiography and ventriculography The electrocardiogram would become more valuable if the correlation of pathologic Q waves with both coronary pathology and ventriculographic data was known and was meaningful This knowledge could influence the selection of patients for angiocardiographic study

The electrocardiogram records depolarization and repolarization of the myocardium Therefore it would be expected to reflect myocardial injury rather than coronary pathology although the two are obviously closely related Critical or even complete coronary occlusion might not produce myocardial injury provided that collateral circulation was adequate to protect myocardial integrity It is not uncommon to find complete proximal occlusion of a coronary artery with adequate retrograde filling The area of myocardium thus supplied may contract normally In such situations the electrocardiogram may be normal reflecting the state of the myocardium rather than the coronary arteries Martinez Rios and associates[4] found 21 cases of normal electrocardiograms and complete occlusion of one or more of the three major coronary arteries They hv

pothesized that this was related to the development of collateral vessels They make no reference to ventricular function

A popular method of evaluating coronary artery disease has been to categorize the patients as having single , double , or triple vessel disease We do not think that this is a valid approach to the presence or absence of Q waves in the electrocardiogram or to the contractile state of the myocardium A regional analysis is required to obtain that information Thus, for example, myocardium in the distribution of the anterior descending coronary artery is not affected by the presence absence or severity of disease in other coronary vessels, except as they may supply collateral circulation

It is our belief that the state of the myocardium is the critical determinant relative to the presence or absence of Q waves The present study was undertaken to determine (1) whether significant Q waves might, in fact, correlate better with ventriculographic abnormalities than with coronary artery pathology, and (2) whether a normal electrocardiogram in the presence of critical coronary artery disease might be indicative of normal ventricular contractility The latter point is of considerable importance since the mortality and morbidity of coronary artery bypass operations depend to a considerable extent upon preoperative ventricular function [13, 14]

The limitations of the study must be considered Although the right anterior oblique projection is the most commonly used view for ventriculographic analysis [15] it does not permit complete evaluation of left ventricular contractility The ventricular septum and the lateral wall are parallel to the plane of the film and hence cannot be assessed This eliminates correlation with the obtuse marginal branches of the circumflex coronary artery and places some limitation on evaluation of the left anterior descending coronary artery

Three regions of the myocardium can be evaluated on the ventriculogram These are the anterior and inferior walls and the apex Two of these areas the anterior wall and the apex, receive their blood supply from the left anterior descending coronary artery Therefore, each area must be correlated with abnormalities in that particular vessel The inferior wall has a variable blood supply, depending on whether the coronary circulation is balanced or the right or circumflex coronary artery is dominant This was taken into account in the analyses However, these difficulties limit somewhat the discrete correlation of multiple variables

Other major limitations include the selection of appropriate combinations of electrocardiographic leads to represent the anterior and inferior walls and the proper grouping of the various abnormalities of ventricular wall motion on ventriculography The former problem was dealt with by selecting several lead variations and correlating each separately With respect to the inferior wall selection of electrocardiographic leads is less difficult since Leads II, III, and aV_F are universally considered to be a reflection of this surface The anterior wall and apex, however, present a more difficult problem since there is less general agreement as to the electrocardiographic correlates of an anterior or apical infarction

Grouping of the abnormalities of ventricular wall motion was done in accordance with the following considerations For each of the three areas that could be evaluated, four possibilities existed normal hypokinetic, akinetic, and dyskinetic, by the definition of Herman and coworkers [11] An akinetic or dyskinetic segment was considered likely to consist mainly of scar tissue It seems probable that hypokinetic regions contain more viable muscle than akinetic or dyskinetic segments If that were so, akinetic and dyskinetic segments could be expected to result in pathologic Q waves The electrocardiogram reflecting hypokinetic regions might be expected to be more variable Although we view this as an appealing theoretical correlation, such clinical pathologic correlations have not been confirmed For this reason we have correlated electrocardiographic findings with the presence or absence of any ventriculographic abnormality Data obtained in the present study indicate that the electrocardiogram is not selective enough to differentiate hypokinesis from akinesis or dyskinesis Grouping all ventricular abnormalities together eliminates this problem

The correlation of pathologic Q waves with coronary arteriographic and ventriculographic findings is summarized in Fig 1 Each of the three myocardial regions being evaluated is listed separately Leads II III, and aV_F were used to evaluate the inferior wall Significant Q waves in Leads V_1 to V_4 were selected as representative of anterior and apical wall infarctions irrespective of

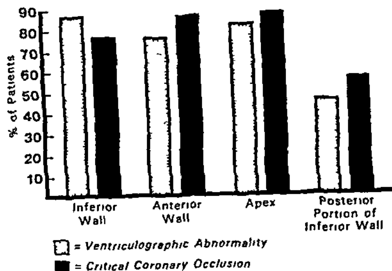


Fig 1 Graphic depiction of percentage of patients with ventriculographic abnormality (*stippled columns*) and critical coronary occlusion (*solid columns*) grouped by region of left ventricle involved No significant difference is demonstrated at the 0 05 level.

whether Q waves were or were not present in Leads V_3 or V_4 The fourth column in this figure represents an attempt to assess the electrocardiographic features (RTR abnormality in Leads $V_{1,2}$) of true posterior myocardial infarction

It is apparent that electrocardiographic features of infarction correlate about equally well with ventriculographic abnormalities and with critical coronary occlusion This correlation ranges from 77 to 87 per cent with the exception of the true posterior site where it is only 55 per cent

With respect to inferior infarction the present study demonstrates increased diagnostic accuracy when Q waves are present in each of the three appropriate leads i e Leads II III and aV_F Forty three per cent of the subjects having a Q wave in Lead III alone demonstrated inferior wall ventriculographic abnormalities If significant Q waves were present in both Leads III and aV_F 69 per cent had ventriculographic abnormalities However when each of the three leads contained a significant Q wave 87 per cent of the subjects had ventricular dysfunction (Fig 2) A similar trend is present when the electrocardiographic findings are correlated with critical coronary occlusion but it is not so striking (Fig 3)

Similar correlations are not so easily drawn for anterior and apical wall segments A significant Q wave encountered only in Lead V_1 may be secondary to septal infarction alone In such cases ventriculographic abnormalities are likely to be undetectable in the right anterior oblique projection Thus our data are insufficient to determine whether a significant Q wave in Lead V_1 has a greater or lesser correlation with anterior infarction than do significant Q waves in Leads V_1 to V For this reason as well as for others noted earlier correlations similar to those made for the inferior wall have not been made for the anterior wall

Tall R waves in Leads $V_{1,2}$ were correlated with true posterior infarction This electrocardiographic configuration can be considered to be analogous to a Q wave in areas of the myocardium where direct electrocardiographic reflection is possible The only anatomically true posterior left ventricular myocardium is the posterior portion of the inferior wall as seen in the right anterior oblique projection The correlation of the electrocardiographic findings with ventriculographic abnormality was 55 per cent and with critical coronary occlusion of the vessels supplying the posterior wall 55 per cent The relatively poor correlation of tall R waves in the right precordial leads may be secondary to normal variation in septal depolarization as well as to cardiac position thereby affecting the relative size of these electrocardiographic deflections In addition there is considerable anatomic variation in the region where the inferior wall joins the

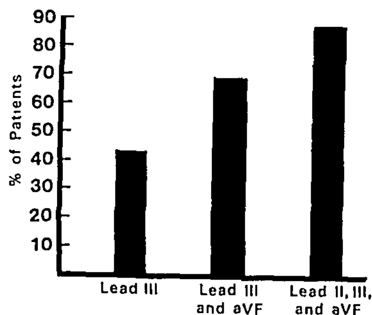


Fig 2 Percentage of patients with inferior wall abnormality grouped according to various combinations of inferior electrocardiographic leads No significant difference is found between Lead III alone and Leads III and aV_F in combination ($p > 0.05$) When Leads III and aV_F are compared to Leads II III and aV_F a significant difference is found ($p < 0.05$) and when Lead III alone is compared to Leads II III and aV_F an even more significant difference ($p < 0.01$) is found

mitral valve ring This results in a variable amount of left ventricular myocardium being in the anatomic true posterior position Indeed in some cases no such myocardium could be identified

Two hundred and sixty nine (54 per cent) of the patients in the study had no significant Q waves (Table V) From 47 to 49 per cent had critical coronary occlusions the remainder had coronary occlusions greater than 50 per cent but less than 75 per cent However 71 to 78 per cent had normal ventriculograms depending upon which region was being evaluated These findings support the contention that a normal electrocardiogram in subjects with coronary artery disease correlates better with normal ventriculographic features than with coronary pathology, and provides an explanation for the finding by Benchimol and associates[16] of normal electrocardiograms in the presence of severe triple vessel disease

The conclusions are that (1) significant Q waves correlate equally well with ventriculographic abnormalities and critical coronary occlusions in vessels supplying the involved areas, (2) significant Q waves in Leads II, III and aV_F have an approximately 80 per cent correlation with ventriculographic abnormality of the inferior wall and critical occlusion of the vessel supplying that area, (3) a similar correlation of

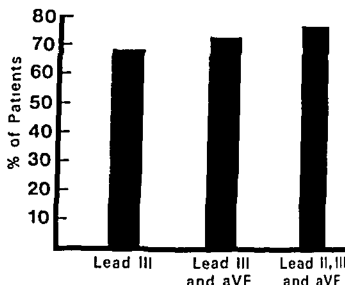


Fig 3 Percentage of patients with critical occlusion of the dominant vessel or the right or circumflex coronary artery in a balanced circulation graphed in accordance with significant Q waves found in various combinations of electrocardiographic leads No significant differences are found ($p > 0.05$)

approximately 80 per cent is found when significant Q waves in Leads V_1 to V_4 are correlated with ventriculographic abnormality of the anterior wall or apex and critical occlusions of the left anterior descending coronary artery (4) electrocardiographic features of true posterior myocardial infarction show an approximately 50 per cent correlation with ventriculographic abnormalities and critical occlusion and (5) subjects with critical coronary artery disease and normal electrocardiograms have normal ventriculographic findings in 71 to 78 per cent of the cases, depending on the vessel or vessels involved

Summary

Four hundred and ninety two patients with coronary artery disease underwent analysis of their electrocardiograms coronary arteriograms, and ventriculograms Significant Q waves were correlated with critical coronary occlusions (≥ 75 per cent obstruction) and ventricular contractility It was found that Q waves correlate equally well with ventriculographic abnormalities and critical coronary occlusions The Q wave correlation varied from 77 to 87 per cent depending on the area of myocardium under consideration, except for true posterior myocardial infarction which correlated 55 per cent with ventriculographic abnormalities and 55 per cent with critical coronary occlusions Significant Q waves in Leads II III, and aV_F are better indica

tors of ventriculographic abnormality than in Leads III and aV_F alone whereas Q waves in the latter two leads are more definitive than in Lead III alone Patients who have critical coronary occlusions and normal electrocardiograms have normal ventriculograms in 71 to 78 per cent of the cases again depending on the area of the myocardium under consideration Thus the normal electrocardiogram correlates better with the ventriculogram than with coronary pathology The abnormal electrocardiogram correlates equally well with both

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Relationships of the tricuspid valve to the membranous ventricular septum in Down's syndrome without endocardial cushion defect Study of 28 specimens, 14 with a ventricular septal defect

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Heart specimens without a ventricular septal defect (VSD) from patients with Down's syndrome have membranous ventricular septa that are enlarged compared to normal a finding that may be an internal stigma [1] In the present study we describe the adjacent portion of the tricuspid valve in specimens with and without a VSD There was an increased incidence of absence of the commissure between the anterior and medial leaflets in all specimens and a high incidence of aneurysm of the membranous ventricular septum (MeVS) in specimens with associated VSD The potential for left ventricle to right atrial shunting occurred only in specimens where fenestrations in an aneurysm of the MeVS were directed into the right atrium instead of into the right ventricle

Materials and methods

Heart specimens from patients with Down s syndrome were reviewed from the collections of the Armed Forces Institute of Pathology and The Johns Hopkins Hospital There were 28 specimens in which the inflow valves and outflow tracts were within normal limits and the cardiac chambers were of appropriate size In our observations of the MeVS and tricuspid valve, we used normal standards for comparison described for MeVS[2] and tricuspid valve [3, 4] The isolated VSD s present in 14 specimens were of the membranous type, since they did not cut obliquely across the muscle of the left ventricular outflow tract, as noted in VSD of the atrioventricular canal type [5, 6] Although aneurysms at the commissure between the anterior and medial leaflets of the tricuspid valve were grossly similar to tricuspid pouches reported in 18 per cent of specimens with endocardial cushion defect,[7] they were considered composed entirely of the MeVS rather than tricuspid valve tissue when they were attached at the periphery to the usual boundaries of the MeVS

Results

Specimens with intact MeVS In four of the 14 specimens with an intact ventricular septum (29 per cent), the tricuspid annulus crossed the MeVS without being interrupted, and there was a normal commissure between the anterior and medial leaflets of the valve (Fig 1, *A*) In one of these four specimens the annulus of the anteromedial commissure was deviated toward the apex of the right ventricle at the center of the MeVS, thus making the atrial portion slightly larger at the expense of the ventricular portion (Fig 1 *B*) A raphé under this depression in the annulus

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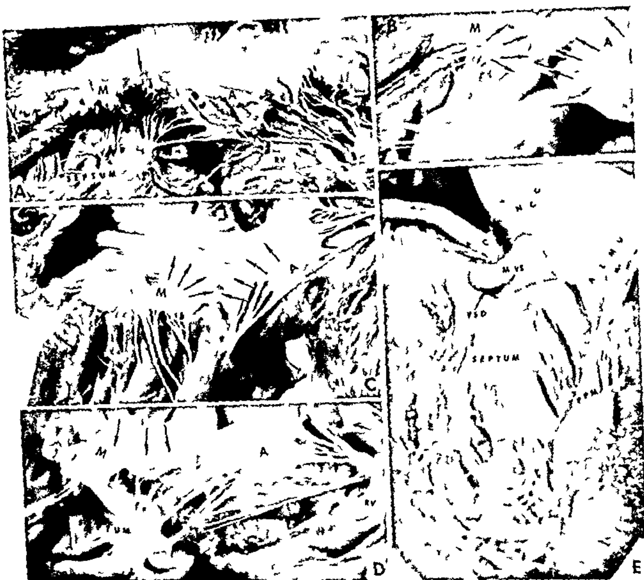


Fig 1 Views (*A* to *D*) from the right side of the heart in Down's syndrome with tricuspid valve cut open to reveal parts of right atrium and ventricle (*A*) In 4 of 14 specimens without a VSD a straight annulus of the tricuspid valve bisected the membranous ventricular septum (*MeVS* arrow) and the anterior (*A*) and medial (*M*) leaflets had fused to form an uninterrupted annulus *RV* right ventricle In the other 10 specimens without a VSD the commissure between the anterior and medial leaflets was absent at the center of the MeVS (*B*) In this specimen the probe is in the pocketlike attachment of the medial leaflet to the MeVS (left arrows) The anterior leaflet was attached to the MeVS by cords and membrane (right arrows) The annulus is deviated toward the valve interruption at the center of the MeVS (*C*) In this specimen the interruption in the valve leaflet was only 2 mm but the annulus was widely deviated toward the apex (arrows) below the enlarged MeVS (*D*) In 5 of 14 specimens with a VSD a straight annulus of the tricuspid valve bisected the MeVS and there was a normal commissure (arrows) (*E*) In 9 of 14 specimens with a VSD the commissure between the anterior and medial leaflets had failed to form In this view of the left ventricle the small VSD is shown in relation to the rest of the MeVS and right and noncoronary cusps of the aortic valve (*RCC NCC*) *ALMV* anterior leaflet of mitral valve *PPM* posterior papillary muscle *MeVS* membranous ventricular septum

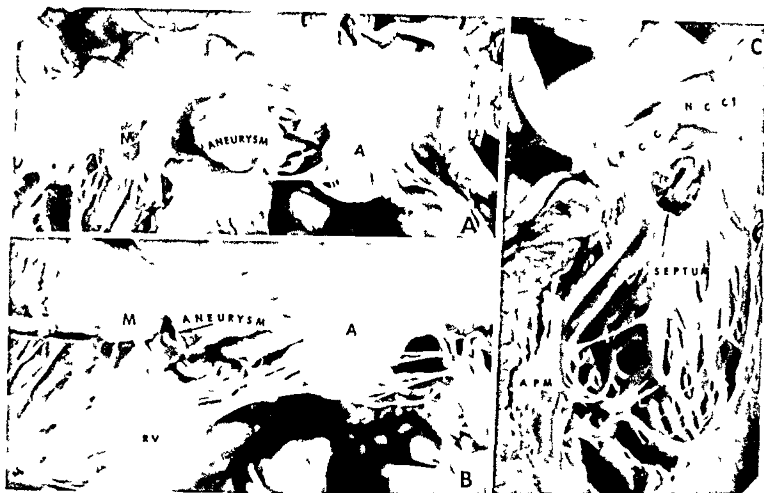


Fig 2 Views of right side of the heart from patients with Down's syndrome with tricuspid valve cut open to reveal parts of right atrium and ventricle (*A*) In this specimen with a VSD a fenestrated aneurysm of the MeVS bulged into the right ventricle separating the anterior (*A*) and medial (*M*) leaflets of the tricuspid valve (*B*) One of the fenestrations in the aneurysm of the MeVS in this specimen (arrow) was directed so that it could conceivably have caused some left ventricle to right atrial shunting *RV* right ventricle (*C*) View of left ventricle to show position of the MeVS in relation to muscular septum and right and noncoronary cusps of the aortic valve (*RCC NCC*) Although the fenestrated aneurysm that resulted was clearly composed of MeVS along its anterior superior and posterior margins its inferior margin blended with the anterior leaflet of the tricuspid valve (arrow) *APM* anterior papillary muscle

supported the underside of the commissure between the anterior and medial leaflets In the other 10 specimens (71 per cent) the annulus was not only deviated toward the apex of the right ventricle but interrupted at the base of the deviation (Fig 1, *C*) This finding was not considered abnormal because it occurs in 16 per cent of normal hearts[3] Like normal specimens with this anatomical variation,[3] valve regurgitation through the interrupted portion of the valve was prevented by pocketlike portions of the anterior and medial leaflets that were attached to the deviated tricuspid annulus and the MeVS (Fig 1, *C*)

Specimens with a VSD of the MeVS In five of the 14 specimens (36 per cent) with a VSD confined to the MeVS the tricuspid annulus crossed the MeVS without being interrupted, and there was a normal commissure between the anterior and medial leaflets of the valve (Fig 1, *D*) The VSD was a communication between left and right ventricles, and aneurysms were not present In three of these five specimens the VSD occupied the entire area of the ventricular portion of the MeVS in one specimen the VSD was quite large but a rim of tissue that probably represented a remnant of the MeVS was still present under the tricuspid annulus and in the other specimen the VSD was small (2 mm in diameter) and located along the inferior border of the MeVS

In nine of the 14 specimens with a VSD (64 per cent), the commissure between the anterior and medial leaflets of the tricuspid valve was absent

In eight of these an aneurysm of the MeVS bulged into the right ventricle (Fig 2 *A*) in six of these eight specimens the aneurysm was attached along its periphery to the usual boundaries of the MeVS[2] and the VSD consisted of fenestrations in the aneurysm (Fig 2 *B*) In the other two of these eight specimens the aneurysm was attached along much of its periphery to what is usually the superior posterior and a portion of the inferior boundaries of the MeVS[2] elsewhere along its periphery it blended with the anterior leaflet of the tricuspid valve instead of the crest of the muscular septum (Fig 2 *B*) In these two specimens then the large VSD could have developed because of a large fenestration in the MeVS that extended all the way to the crest of the muscular septum or incorporation of a portion of the anlage for the MeVS into the tricuspid valve instead of union to the crest of the muscular ventricular septum In three of the specimens with fenestrated aneurysm at least one of the openings was directed toward the right atrium apparently the result of tilting or bulging of the aneurysm into the space between the interrupted tricuspid annulus (Fig 2 *C*) In these three specimens left ventricle to right atrial shunting may have been present during life

In the remaining specimen with absent commissure the single VSD was small (2 mm in diameter or about 5 per cent of the area of the MeVS Fig 1 *E*) and located along the inferior border of the MeVS This VSD was a communication between the outflow tract of the left ventricle and right ventricle just under the pouchlike medial margin of the anterior leaflet of the tricuspid valve There was no aneurysm in this specimen presumably because the VSD was unrelated to the interrupted portion of the tricuspid annulus

Discussion

Absent commissure of the tricuspid valve results when the dextrodorsal conus swelling or right bulbar ridge [4] (anlage for the adjacent portion of the anterior leaflet) fails to unite with the atrioventricular cushion tissue[5] that is the anlage of the medial leaflet In Down's syndrome the enlargement of the MeVS could certainly contribute to the increased incidence of nonunion of these ridges and swellings But the enlargement of the MeVS is in turn probably the result of a basic structural anomaly at the base of the heart such as malalignment or maldevelopment of the ventricular septum [1] [11]

It is curious that aneurysms in these specimens were present only when the commissure was absent Perhaps flow or turbulence through a fenestrated MeVS produces systolic stretching of the MeVS into the space between the tricuspid valve leaflets If so such aneurysms should be considered acquired lesions as systolic flow should occur through the VSD only after the right ventricular pressure drops below that in the left ventricle On the other hand flow produced aneurysms could develop in fetal life if the fenestration was directed into the right atrium where the pressure is considerably less than that in the left ventricle Although unlikely this explanation could conceivably be applied to the three specimens in our study that had fenestrations directed toward the right atrium Serial studies of the formation of aneurysm of the MeVS in patients with and without Down's syndrome should help clarify this point

Summary

The commissure between the anterior and medial leaflets of the tricuspid valve is commonly absent in Down's syndrome without endocardial cushion defect (19 of 28 specimens) As a result aneurysm of the membranous ventricular septum may develop (eight of 14 specimens with ventricular septal defect limited to the membranous ventricular septum) and the potential for left ventricle to right atrial communication is increased

The authors wish to thank Judith Lawson and John Dexter for assistance in the selection of specimens from the Armed Forces Institute of Pathology Irene McQuay Dr Richard Jones Dr Fima Lifschutz and Dr Kurt Glaser for helping us acquire two specimens from Rosewood State Hospital Owings Mills Md and Gary Sterner for photographs in Figs 1 and 2

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Experimental and laboratory reports

Pulmonary arterial oxygen saturation during treadmill exercise: A discriminative index of functional class

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Evaluation of the functional status of patients with cardiovascular impairment is essential in assessing therapy and determining prognosis. Usually this is done by means of clinical interview, a method confounded by the overzealous or undermotivated patient. Therefore, another method of evaluation that makes use of a known workload and a measurable end point should provide objective data and aid in assigning functional class. The capacity to do exercise, a measure of the functional status of a patient, is a function of the interrelationships between oxygen consumption, cardiac output, and peripheral oxygen extraction. In normal individuals during exercise there is an increase in the total oxygen consumption and an expansion of the arteriovenous oxygen difference in response to a given rise in cardiac output. In patients with advanced heart disease, a disproportionate widening of the arteriovenous oxygen difference occurs in relation to the increased oxygen consumption and cardiac output. This increase in arteriovenous oxygen difference is almost wholly reflected in the pulmonary arterial oxygen saturation. Accordingly, the determination of pulmonary arterial oxygen saturation during treadmill exercise has been shown to separate normal from abnormal individuals.[1] Since varying degrees of functional impairment must also be identified, the purpose of this study was to determine whether pulmonary arterial oxygen saturation during graded treadmill exercise could be used to separate functional classes II and III of the New York Heart Association's[2] classification, clinically the most important, yet at times the most difficult to distinguish.

Materials and methods

Seventeen patients with heart disease, 11 females and 6 males, were interviewed by senior attending physicians and classified according to the New York Heart Association (Table I). Six were in functional class II and 11 were in functional class III. 14 patients had rheumatic valvular disease, 2 had idiopathic cardiomyopathy, and 1 had idiopathic hypertrophic subaortic stenosis. A history of angina pectoris was not elicited in any patient, nor was anyone considered to have pulmonary parenchymal disease. Nine patients were in sinus rhythm and 8 had established atrial fibrillation. All clinical diagnoses were confirmed by cardiac catheterization. No patient with an intracardiac shunt was studied.

The study was performed with the patients in the postabsorptive state after a physical examination and the recording of a 12 lead electrocardiogram. A simulated electrocardiographic Lead V_5 was attached and monitored during rest and exercise. After a practice walk on the motor driven treadmill (Quinton Model 1849C), patients

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ingly the determination of pulmonary arterial oxygen saturation during treadmill exercise has been shown to separate normal from abnormal individuals.[3] Since varying degrees of functional impairment must also be identified the purpose of this study was to determine whether pulmonary arterial oxygen saturation during graded treadmill exercise could be used to separate functional classes II and III of the New York Heart Association's[4] classification clinically the most important yet at times the most difficult to distinguish

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Table I Clinical data

FC	Patient No	Age (yr)	Sex	Diagnosis	Rhythm	Digitalis
II	1	20	M	IHSS	RSR	Yes
	2	48	M	Cardiomyopathy idiopathic	RSR	Yes
	3	43	M	RHD AI MI	RSR	Yes
	4	20	F	RHD MI	AF	No
	5	52	M	RHD AI MI	RSR	Yes
	6	33	F	RHD MS MI AI	RSR	Yes
III	7	48	M	RHD MS	AF	Yes
	8	57	M	RHD Aortic valve prosthesis (AS)	RSR	
	9	57	M	RHD MI MS AI	AF	Yes
	10	49	M	RHD MI MS AI	AF	Yes
	11	37	F	RHD MS MI AI	AF	Yes
	12	47	M	RHD MS MI	RSR	Yes
	13	42	F	RHD MS AI AS	AF	Yes
	14	24	F	RHD MS MI	RSR	No
	15	48	M	Cardiomyopathy idiopathic	RSR	Yes
	16	28	F	RHD MS	AF	Yes
	17	56	M	RHD MS	AF	Yes

Abbreviations AF = atrial fibrillation AI = aortic valve insufficiency AS = aortic valve stenosis FC = New York Heart Association functional class IHSS = idiopathic hypertrophic subaortic stenosis MI = mitral valve insufficiency MS = mitral valve stenosis RHD = rheumatic heart disease RSR = regular sinus rhythm

were placed in the supine position and by means of the technique of Swan and associates a No 7F balloon tipped catheter was advanced from the basilic vein to the main pulmonary artery [7] The catheter was connected to a Statham P23db strain gauge and pulmonary arterial systolic diastolic, and mean pressures, along with a simulated electrocardiographic Lead V_5 were amplified and displayed on a Hewlett Packard multichannel oscilloscope For a zero reference pressure the transducers were placed at the level of the atria the fourth intercostal space anteriorly, and the catheterized arm was supported horizontally, at rest and during exercise The systemic blood pressure was obtained with a pneumatic cuff by auscultation of Korotkoff sounds The blood pressure was taken and the pulmonary arterial pressure and electrocardiographic Lead V_5 were recorded with the patient in the upright position The patient inhaled from a gasometer filled with room air and ventilation was measured from kymographic recordings Samples of expired air were collected in Douglas bags for 3 minutes at rest in the upright position and during the last minute of each level of exercise The

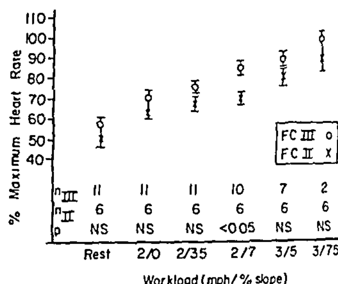


Fig 1 The mean percentage maximum heart rate is shown at each workload for the patients able to complete that level of exercise *Abbreviations* FC = New York Heart Association functional class n_{II} = number FC II n_{III} = number FC III X = mean ± 1 SEM for FC II 0 = mean ± 1 SEM for FC III

oxygen and carbon dioxide concentrations in the expired air were quickly determined with a Beckman 73 paramagnetic oxygen analyzer and Beckman 215A infrared carbon dioxide analyzer, respectively The true oxygen consumption was calculated according to the method of Haldane and Priestley [8] Samples of blood from the pulmonary artery were analyzed with a Beckman Du 2 spectrophotometer in order to determine the percentage of oxygen saturation by the method of Hickman and Frayser [9] Patients were exercised intermittently, walking 4 minutes and resting 3 minutes Thus beginning at 2 mph and zero grade, the speed and/or slope were altered so as to increase the oxygen consumption one multiple of the resting value for each progressive level of work [10] During the last minute of each level of exercise recordings and sample collections were obtained All patients were exercised to fatigue In no instance did chest pain or electrocardiographic changes require the test to be terminated prior to this end point Percentage maximum heart rate for age and percentage change in pulmonary arterial end diastolic pressure from rest to each workload were calculated [11]

The data reported are mean values ± one standard error of the mean, comparisons were made by means of the Student s unpaired t test and p values of less than 0 05 were considered to be significant

Table II

Workload	FC	n	VO	HR	% Max HR	BP	PAP	% PA EDP	PAO
Rest	II	6	3 8 ± 0 3	93 ± "4	50 ± 3 8	125/67 ± "/6	20 ± 5 0		64 ± 1 4
	III	11	3 8 ± 0 1	104 ± 8 1	57 ± 4 6	1?6/80 ± 5/4	26 ± 2 0		56 ± 1.9
2/0	II	6	10 4 ± 0	116 ± 6 8	6? ± 3 0	129/"0 ± 13/5	29 ± 6 8	93 ± 6 7	50 ± 2 1
	III	11	10 0 ± 0 5	126 ± 8	"0 ± 3 4	129/80 ± 5/5	49 ± 5.5	164 ± "0	39 ± 0 9
2/3.5	II	6	12 8 ± 0 5	1.4 ± 7.2	68 ± ?9	137/73 ± 11/6	34 ± 7 1	138 + 4 8	44 ± 2 1
	III	11	11.8 ± 0 6	14? ± 8 1	77 ± 3 8	13 /8 ± 4/4	57 ± 6 7	198 ± 5 6	34 ± 0 9
2/7	II	6	15 5 ± 0 6	131 ± 8 0	72 ± 4 0	14?/"5 ± 14/5	38 ± 7 6	174 ± 4 0	39 ± 1.2
	III	11	13 9 ± 0 5	151 ± 8 1	83 ± 3 5	143/84 ± 5/4	63 ± 7 4	221 ± 8 0	28 ± 1 1
3/5	II	6	19 9 ± 0 6	153 ± 6 7	8? ± 3 4	153/ 2 + 15/5	40 ± 7 1	215 ± 9 9	34 ± 1 1
	III	7	17 7 ± 0 3	1.6 ± 7 9	91 ± 4 0	154/91 ± 3/8	"2 ± 12.3	?40 ± 2.5	?6 ± 0 8
3/7 5	II	6	22 4 ± 0	166 ± 6 4	91 ± 3 7	1.9/83 ± 11/6	44 ± 11 0	24? ± 5 0	31 ± 1 0
	III	2	?0 3 ± 0 1	16? ± 1? 5	100 ± 8 0	160/"0 ± 0/0	8? ± 17 0	266 ± 9 0	2. ± 0 9

Abo e alues represent group m s ± S E M Workl ad = t e dmill spe d and per cent slope (mph/% l pe) n = number of patients studied VO = oxyg n consu mpt n (c c O /Kg /min) HR = heart rate (beats/min) % Max HR = per cent of predicted maximum heart rate BP = systolic and dia t l art rial blood pressure (m m Hg) PAP = mean pulmona y rterial pressure (m m Hg) % PA EDP = pe cent h nge in pulmonary arteri l end-d astolic pressure fr m rest pressure PAO = per cent xyg n satur tion in pulm nary rterial blood sample (%) F C = New York Heart Associat on funct nal class

Indi tes s gn ficant p lue

Table III Individual treadmill exercise responses at a speed of 2 mph and 7 per cent slope

Patient No	VO	HR	% Max HR	BP	PAP	% PA EDP	PAO
1	19 1	130	6.	8./70	18	190	
2	13.1	104	60	135/8.	.5	16.	43
3	14 9	13.	81	160/80	38	183	39
4	15 5	13?	6f	134/8f	9	169	36
5	16 ?	1?5	4	190/50	5?	1/1	41
6	15 4	165	8.		68	166	.8
X̄	15.5	131	2	14?/ 5	38	1 4	.9
S E M	± 0 6	± 8 0	± 4 0	± 14/5	± 7 6	± 4 0	+ 1 2
	15 .	155	89	160/110	50	2/ 3	30
8	16 5	118	2	150/80	45	?14	34
9	15.3	16?	100	130/ 0	75	215	29
10	15 0	1..	83	150/8.	6?	181	3
11	11 1	197	86				24
1	13 4	161	93	160/85	90		2.
13	14 6	149	83	1.0/90	107	216	31
14	14 6	14"	"3		38	?24	3?
15	11 3	1?9	"4		3?	??9	26
16	11 5	18.	91	120/ 0	68		25
1.	14 1	10.	64	130/85	58	231	26
X̄	13 9	151	83	143/84	63	2 1	.8
S E M	+ 0 5	8 1	± 3 5	± 5/4	± . 4	± 8 0	± 1 1

Abbreviations as in T bl II

Results

Oxygen consumption The oxygen consumption progressively increased with each work level in both groups (Table II) Except for oxygen consumption at a treadmill speed of 3 mph and 5 per cent slope there was no significant difference in mean values at rest or with any other level of exercise Since patients in functional class II were able to complete higher work levels than those in functional class III the peak oxygen consumption was higher for functional class II (22 4 c c O /Kg /min) than for functional class III (15 4 c c O_2/Kg /min) ($p < 0\,001$)

Heart rate The heart rate for both classes progressively increased with exercise (Fig 1) At a treadmill speed of 2 mph and 7 per cent slope the maximum heart rate for patients in functional class III was 83 per cent and for functional class II 72 per cent ($p < 0\,05$) However considerable overlap of individual values at this and other levels of exercise occurred (Tables II and III)

Systemic blood pressure The mean systolic and mean diastolic pressures progressively increased with exercise There was no difference in systemic blood pressure between the two functional classes at any work level (Table II)

Pulmonary arterial pressure No difference was observed between the two functional classes in systolic or diastolic pulmonary arterial pressure except for values obtained at a treadmill speed of 2 mph and zero grade However mean pulmonary arterial pressures were significantly different during treadmill exercise from 2 mph and zero grade to 3 mph and 5 per cent grade (Table II) The percentage change in pulmonary arterial end-diastolic pressure showed differences similar to those for the mean pulmonary arterial pressure (Fig 2)

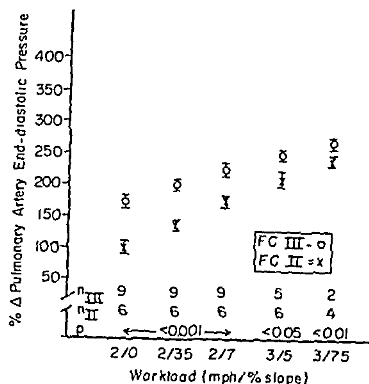


Fig 2 The end-diastolic pressure at each work level is compared to the resting value and recorded as the mean percentage change The pulmonary arterial end diastolic pressure at rest for F C II was 16 ± 4 mm Hg and 22 ± 2 mm Hg for F C III (p > 0 1) Abbreviations are as in Fig 1

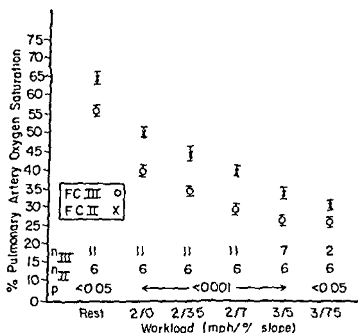


Fig 3 The mean pulmonary arterial oxygen saturation plotted against workload Abbreviations are as in Fig 1

Pulmonary arterial oxygen saturation The pulmonary arterial oxygen saturation decreased progressively with exercise (Fig 3) The difference in mean values was significant at rest and at each work level (Table II) At a treadmill speed of 2 mph and 7 per cent slope a workload achievable by both groups all patients in functional class II had a pulmonary arterial oxygen saturation above 36 per cent, and all patients in functional class III had lower values (Table III) At higher treadmill workloads, the pulmonary arterial oxygen saturation also separated all patients in the two functional classes however, 4 of the 11 patients in functional class III were unable to perform this amount of exercise

Discussion

Pulmonary arterial oxygen saturation is influenced by cardiac output and peripheral oxygen extraction, two determinants of exercise tolerance Epstein and co workers[9] demonstrated that the pulmonary arterial oxygen saturation, when correlated with cardiac output is a good indicator of cardiac performance at nearly maximal work loads In this study, the pulmonary arterial oxygen saturation provided separation of both functional classes at rest and during exercise with a complete division of the patients at a treadmill speed of 2 mph and 7 per cent slope and beyond

We also examined the use of oxygen consumption, heart rate, and pulmonary arterial pressure during treadmill exercise, as means of separating functional class II from class III Comparing the rates of peak oxygen consumption during exercise, Patterson and co workers[10] found that patients in functional class II had consumed 16 to 22 c c O_2/Kg /min , and those in functional class III 10 to 16 c c O_2/Kg /min The peak oxygen consumptions of our patients in functional classes II and III were similar, with means of 22 4 and 15 1 c c O_2/Kg /min , respectively However, as in the preceding study individual overlap occurred Rather than using the peak performance we examined all data at the same treadmill workload of 2 mph and 7 per cent slope since patients in both functional classes could be expected to complete this level of exercise The oxygen consumptions for functional classes II and III at this level of exercise were similar The percent maximum heart rates were significantly different, but there was considerable overlap and heart rate alone would not allow practical discrimination of individual patients The systolic and diastolic pulmonary arterial pressures provided little help in differentiating between the two groups Although mean pulmonary arterial pressures had differed significantly between the two groups at several work levels overlap again occurred In

evaluating the change in pulmonary arterial end diastolic pressure from rest to each work level we found a significant difference between the responses of the two groups This has been anticipated since the pulmonary arterial pressure during exercise reflects the response of the pulmonary vasculature interposed valvular disease and the response of the left ventricle to an increased workload. Although some of the above mentioned parameters separated the two groups only the pulmonary arterial oxygen saturation showed no individual overlap

Despite the small number of patients in each functional class the groups were homogeneous on the basis of peak oxygen consumptions which were similar to those of a larger number of patients in the same functional classes undergoing similar exercise [9] Eight patients had rheumatic heart disease with atrial fibrillation Most patients with this rhythm are in functional class III and probably reflect more severe heart disease Atrial fibrillation is usually associated with a more rapid ventricular rate during exercise than is sinus rhythm but does not however significantly restrict exercise tolerance when the resting ventricular rate is controlled [2] This method of evaluation will have to be tested in a larger group of patients in order to establish its general value in separating functional classes

Summary

Six patients in functional class II and 11 in functional class III underwent graded treadmill exercise with severe fatigue as their limiting symptom During exercise none of the patients developed chest pain or significant arrhythmia Our data suggest that at a treadmill workload of 2 mph and 7 per cent slope with an oxygen consumption four times that at rest measurement of the pulmonary arterial oxygen saturation permits clear separation of functional class II from functional class III Although there was a significant difference in the heart rate response mean pulmonary arterial pressure and percentage change in pulmonary arterial end-diastolic pressure considerable overlap occurred The use of pulmonary arterial oxygen saturation may prove to be of value in instances in which the functional cardiac status is not reasonably clear from the clinical interview or routine exercise testing It requires less than maximal effort on the part of the patient and provides an objective end point to distinguish between two important groups of patients

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Encephalomyocarditis (EMC) virus infection of the femoral vein of newborn mice

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The encephalomyocarditis (EMC) virus is highly cardiotropic in newborn mice[1-4] and infects major[5] and minor[6] blood vessels as well as the endocardium[7] and valves[8] of the heart In addition the EMC virus has been shown to infect the kidney,[9] liver[10] and pancreas[11,12] of mice The EMC virus like other picornaviruses, elicits a cellular pathology in all these tissues that is characterized by the presence of numerous membrane-vesicle complexes dilatation of rough endoplasmic reticulum and margination and pyknosis of nuclear chromatin Inflammation often accompanies picornaviral infection

In order to learn more about viral infections of blood vessels, we studied arteries and veins of newborn mice infected with EMC virus This report describes the electron microscopic findings in the femoral veins of these mice

Methods and materials

Six newborn mice of a random HaM/ICR strain were studied One of the six mice was inoculated with virus free culture fluid to serve as a control The other five mice were inoculated intraperitoneally with 0 05 ml EMC virus culture fluid (10^{6} $TCID_{50}$) and killed 24 hours later The entire leg containing the intact femoral vessels was excised and the skin and muscle were trimmed away to expose the blood vessels to the fixative solution The leg was fixed in 3 per cent phosphate buffered glutaraldehyde for three hours The tissues were then rinsed with six changes of fresh buffer and left in fresh buffer overnight, after which excess tissues and bone around the femoral vessels were carefully trimmed away under a dissecting microscope The above preparation helped to eliminate technical artifacts due to damage by mechanical handling The tissues were post fixed in cold 1 per cent osmium tetroxide in phosphate buffer for 1 5 hours Dehydration was initiated in 50 per cent methanol The vessels were processed through a series of ascending concentrations of cold methanol followed by final dehydration in three rinses of absolute methanol at room temperature Embedment was in epoxy resin in flat molds to assure cross sectional orientation for sectioning Thick epoxy sections were stained with toluidine blue Selected areas were trimmed of excess tissue so that only the femoral vein remained for thin sectioning Thin sections were stained with uranyl acetate and lead citrate and examined with a Siemens Elmiskop I electron microscope

Results

Control mouse The wall of the femoral vein of the control mouse consisted of an endothelial layer of single cell thickness a loosely constructed tunica media with one to several layers of smooth muscle cells and a tunica adventitia composed of several layers of loosely intertwining fibroblasts and fibrous bundles There was no clear line of demarcation between the layers In cross section the elastica appeared as rods oriented in the longitudinal axis of the vein (Fig 1) Fibroblasts could be distinguished from smooth muscle cells by the presence of abundant rough endoplasmic reticulum and the absence of myofilaments common to smooth muscle cells

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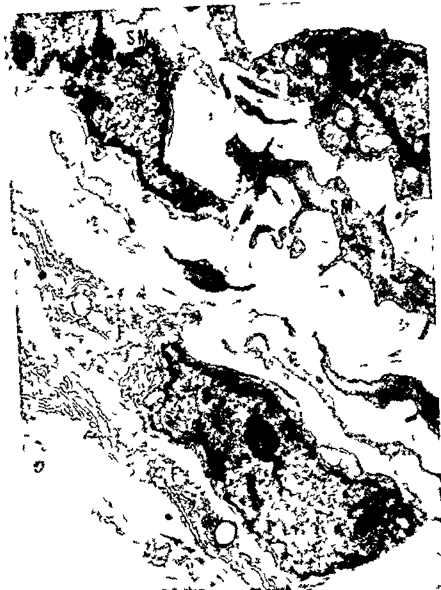


Fig 1 Portion of the wall of the femoral vein of a newborn mouse injected with virus free control fluid and killed 24 hours later The intima is composed of a single cell endothelial layer (*EN*) Smooth muscle cells (*SM*) containing myofilaments make up the tunica media Fibroblasts (*F*) comprise the tunica adventitia The fibroblasts contain abundant rough endoplasmic reticulum (Original magnification ×15 000)

EMC virus infected mice The endothelial cells of veins of the viral infected mice were frequently disrupted (Figs 2 and 3) with the mitochondria swollen and sometimes containing vacuoles (Fig 3) Smooth muscle cells were frequently disrupted and contained numerous membrane-vesicle complexes of cytonecrosis common to picornavirus infected cells (Figs 2 and 3) Nuclear pyknosis within smooth muscle cells was occasionally observed (Fig 3) Also margination of chromatin was frequently encountered

The adventitial fibrous bundles of collagen and collagen bundles comprising the surrounding loose connective tissue were commonly severely disrupted In three of the animals studied viral crystalline aggregates were observed in adventitial fibroblasts (Fig 4) and fibroblasts of the loose connective tissue The viral crystals were frequently associated with typical picornavirus cytonecrosis consisting of the formation of membrane-vesicle complexes and dilatation of rough endoplasmic reticulum (Fig 4)

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Fig 3 Another area of the femoral vein wall of the same mouse as in Fig 2 Some of the mitochondria (M) in the endothelial cells are swollen and vacuolated There is a portion of a pyknotic nucelus (N) in the medial smooth muscle cell as well as membrane vesicle complexes (MVC) (Original magnification ×26 000)

ence was related to the slower rate of blood flow in veins than in arteries Smooth muscle cells were found to be affected in the vein but not in the artery However we have shown previously that smooth muscle cells in the aorta of newborn mice are infected with EMC virus and we have observed viral crystals in such cells Because of the small sample size and the small volume of tissue observed electron microscopically it is possible that viral material was present but not encountered in the smooth muscle cells of the femoral veins One wonders from these findings if infection of veins by viruses may be responsible for venous thrombosis so commonly found in man

Summary

The EMC virus was found to infect and injure the femoral veins of newborn mice EMC viral crystals were found in the adventitial fibroblasts



Fig 2 A portion of the femoral vein wall from a newborn mouse that was inoculated with EMC virus culture fluid and killed 24 hours later The endothelial layer is disrupted and the mitochondria (*M*) are swollen Within the cytoplasm of a medial smooth muscle cell are abundant membrane vesicle complexes (*MVC*) Myofilaments (*MYO*) are still apparent (Original magnification ×20 800)

Discussion

This report shows that encephalomyocarditis (EMC) virus will infect the wall of the femoral vein of the newborn mouse It is therefore, conceivable that other smaller and larger venous vessels may be similarly affected The EMC virus elicits a cytopathic response consistent with other picornaviruses[13 18] in a variety of other tissue types The prominent features of this cytopathic effect are membrane proliferation[14] with the formation of numerous membrane-vesicle complexes and dilatation of rough endoplasmic reticulum Margination of nuclear chromatin and pyknosis of nuclei were also observed However, inflammation as observed previously was not noted in the femoral veins of these animals

The femoral veins of the EMC virus infected animals appeared to have more extensive damage than the femoral arteries[6] of the same animals It may be postulated that one reason for this differ

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Fig 4 A portion of the wall of the femoral vein of an FMC virus infected newborn mouse killed 24 hours after inoculation The endothelium (*EN*) distal to the nuclear region is thin In the tunica adventitia is a fibroblast in which areas of cytonecrosis are apparent (*arrows*) The rough endoplasmic reticulum (*RER*) is dilated in some areas A viral crystal (V) is associated with the cytonecrosis (Original magnification ×21 600) This crystal is shown at greater magnification (×56 000) in the insert

of these veins In view of the extensive damage observed in the extremely small amount of tissue examined electron microscopically the extent of the viral phlebitis must have been considerable The relationship of these findings to the patho genesis of thrombophlebitis in man provokes interesting speculations

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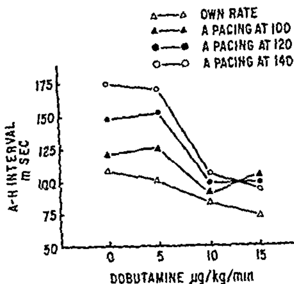


Fig 1 Variations of A H interval during spontaneous rhythm and atrial pacing at progressive concentrations of Dobutamine

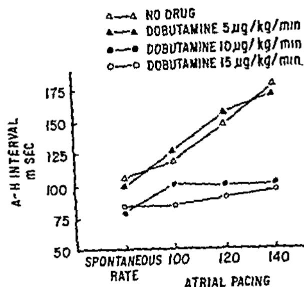


Fig 2 Variations of A H interval at progressive rates of atrial pacing in patients receiving different concentrations of Dobutamine intravenously

Table I Electrophysiologic effects of dobutamine

	No drug	5 µg/Kg/min	10 µg/Kg/min	15 µg/Kg/min
Rate (beats/min.)	74 ± 1.9	78 ± 5 1	99 ± 5 6	113 ± [illegible]4
A H interval (msec.)				
Spontaneous	108 ± 9 7	100 ± 8 5	83 ± 9 4	78 ± 9.3
Pacing–100	120 ± 9 0	1[illegible]5 ± 17	83 ± 16	105 ± [illegible]
Pacing–1[illegible]0	147 ± 7 7	152 ± 21	90 ± 11	98 ± 17
Pacing–140	1[illegible]7 ± 13	171 ± 2[illegible]	95 ± 15	9[illegible] ± 11
H V interval (msec)				
Spontaneous	60 ± 6 9	60 ± 8 1	56 ± 8 7	53 ± 6 7
Pacing–100	60 ± 6 2	57 ± 7.3	51 ± 7.5	50 ± 15
Pacing–120	55 ± 7.2	53 ± 7.8	60 ± 9 4	53 ± 9.3
Pacing–140	54 ± 7 7	54 ± 7 2	57 ± 12	58 ± 9.3

Significantly different from values observed without drug a = $p < 0.01$ b = $p < 0.0$[illegible] = $p < 0.05$
Significantly different from values observed without pacing d = $p < 0.01$ e = $p < 0.0$[illegible] f = $p < 0.05$

Results

The electrophysiologic effects of Dobutamine are presented in Table I and the average dose response curves in Figs 1 and 2

Table I allows for comparison of heart rate and of A H and H V intervals (both during spontaneous rhythm and at atrial pacing rates of 100 120 and 140 per minute) at progressive increments of Dobutamine Comparison of each parameter with basal control is displayed from left to right and statistical significance indicated by the letters a b and c for P values of 0 01 0 02 and 0 05 respectively The effects of atrial pacing upon A H and H V intervals at any given concentration of the drug are displayed in vertical columns and statistical significance in comparison to values obtained without pacing is indicated by the letters d e and f for P values of 0 01 0 02 and 0 05 respectively

Heart rate The mean basal rate did not change with the first concentration of the drug (5 µg per kilogram per minute) A moderate but statistically significant increase was observed with the second concentration (10 µg per kilogram per minute) At the maximal concentration of 15 µg per kilogram per minute the rate increase aver

Effects of Dobutamine on atrioventricular conduction

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Dobutamine a new catecholamine agent with beta stimulating properties is being investigated for its hemodynamic effects in congestive heart failure [1-3]

During the course of these studies[1] we had observed only slight increase in heart rate in patients with sinus rhythm whereas a marked increase in ventricular response was seen in patients with atrial fibrillation The dose range administered in previous investigations had been 2 5 to 10 μg per kilogram per minute

It seemed possible that Dobutamine, like other catecholamines with beta stimulating properties might enhance A V nodal conduction

The purpose of this study using His bundle recordings during administration of Dobutamine was to assess the influence of the drug upon A V conduction

Material and methods

The study group consisted of six patients (three men and three women) whose ages ranged from 22 to 66 years These patients were scheduled to undergo routine diagnostic tests in the hemodynamic laboratory for rheumatic valvular (aortic or mitral insufficiency) or congenital heart disease (atrial septal defect or pulmonary stenosis) None of the patients was in congestive heart failure, or had electrocardiographic evidence of pre existent A V conduction abnormalities Informed consent was obtained from each patient after proper description of the procedure and its aims

Under local anesthesia a quadripolar catheter was introduced percutaneously into the right femoral vein and fluoroscopically positioned at the level of the tricuspid valve Another bipolar catheter was passed via the right antecubital vein and positioned against the lateral wall of the right atrium

His bundle electrograms[4-7] were recorded with the patient's own basal rhythm and during atrial pacing at rates of 100, 120, and 140 per minute

Recordings were repeated following the administration of Dobutamine intravenously by the micro drip technique, at infusion rates of 5 10 and 15 μg per kilogram per minute during consecutive periods of 15 minutes each The tracings were obtained with a PR 12 Electronics for Medicine at paper speed of 100 mm per second

The following intervals were measured in milliseconds (1) A H the interval from the first rapid deflection of the atrial electrogram to the first high frequency component of the His bundle electrogram, reflecting conduction time through the A V node, (2) H V the interval between the first high frequency component of the His bundle electrogram to the earliest initial deflection of the QRS complex on the surface electrocardiogram reflecting conduction time in the His Purkinje system

For each of these intervals, at least 10 beats were averaged both before and during administration of Dobutamine and the mean values were utilized for comparison Statistical analysis and paired t tests for significance were applied to all values obtained

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shortening of A H occurs with an infusion rate of 10 μg per kilogram per minute without obvious further changes at a higher infusion rate

Fig 2 emphasizes the influence of atrial pacing on A H conduction time with and without Dobutamine Increasing heart rate from control to 140 per minute is associated with progressive increment in A H conduction time when no drug is used While the administration of Dobutamine at a rate of 5 μg per kilogram per minute fails to influence the prolongation of A H interval induced by atrial pacing concentrations of 10 and 15 μg per kilogram per minute effectively prevent such prolongation

Fig 3 depicts the typical changes observed in one patient with the administration of Dobutamine marked shortening of the A H interval occurs at similar driving rates

H V interval The H V interval did not change significantly during spontaneous rates or with pacing, at different concentrations of Dobutamine (with the exception of the third concentration of 15 μg per kilogram per minute during spontaneous rhythm)

Discussion

Catecholamines are thought to influence A V conduction in man Objective demonstration of this property has been particularly shown for isoproterenol Wallace and Sarnoff[3] demonstrated that sympathetic nerve stimulation in animals caused significant changes in A V conduction the A H interval was markedly shortened with no effect upon intraventricular conduction (H V interval) Damato and co workers using the His bundle recording technique in man demonstrated that isoproterenol shortens the A H interval without affecting the H V interval Dhingra and co workers[9] not only found shortening in the A H interval but observed facilitation of conduction in the His Purkinje system with administration of isoproterenol

Our study with Dobutamine demonstrates a clear facilitation of A V conduction as depicted in Fig 1 The initial concentration of 5 μg per kilogram per minute did not induce significant changes in the A H interval either during spontaneous rhythm or with atrial pacing however infusion rates of 10 and 15 μg per kilogram per minute shortened the A H interval significantly in comparison with control values Fig 2 presents the data in a different way progressive lengthening of the A H interval takes place as the rate increases which is a well known phenomenon already described[7] The initial concentration of 5 μg per kilogram per minute did not modify such response However Dobutamine at infusion rates of 10 and 15 μg per kilogram per minute kept the A H interval practically unchanged despite the increasing pacing rate This again demonstrates the enhancement of A V conduction produced by the drug

Changes in the H V interval with Dobutamine were small and practically of no statistical significance

No consistent changes could be observed for intra atrial conduction times It is conceivable that shortening of such intervals might take place but further investigation of this aspect would require obtainment of multiple and simultaneous intra atrial recordings not performed in this study

From available data Dobutamine acts as a positive inotropic agent like isoproterenol but with less increase in heart rate and with no induction of arrhythmias[1]

This property coupled with facilitation of A V conduction could make of Dobutamine a useful agent in the management of patients with the combination of heart failure and spontaneous or induced A V conduction abnormalities

Summary

Dobutamine a new beta stimulating catecholamine has been investigated in terms of its effect upon atrioventricular conduction

Bundle of His recordings were obtained on six patients in basal conditions and with right atrial pacing at rates of 100 120 and 140 per minute Recordings were repeated following intravenous administration of Dobutamine in doses of 5 10 and 15 μg per kilogram per minute Dose response curves were thus obtained for A H and H V intervals

Heart rate increased only moderately with progressive concentrations of the drug Very significant facilitation of A H conduction was demonstrated with doses of 10 and 15 μg per kilogram per minute with no effect upon H V times

Dobutamine may be a clinically useful inotropic agent in conditions associated with A V conduction disturbances

We are grateful to Eli Lilly Research Laboratories for making Dobutamine available to us for this investigation

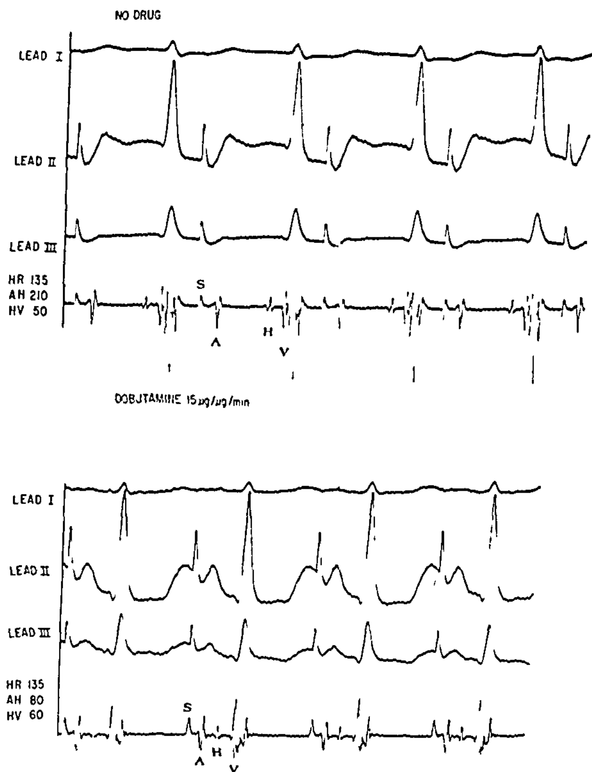


Fig 3 A H conduction time at similar driving rates in patients before (upper) and after (lower) intravenous infusion of Dobutamine Significant shortening of A H interval is observed with no appreciable changes in H V interval *S*=Stimulus artifact

aged 50 per cent above control value Tachycardia was not excessive in any individual patient, was well tolerated and was not associated with ectopic arrhythmias

A H interval All patients had a normal A H interval (less than 130 msec) with a mean of 108 msec The first concentration of Dobutamine did not modify significantly the A H interval either during spontaneous rhythm or at different rates of atrial pacing The second and third concentrations of the drug produced a definite shortening of the A H interval during spontaneous rhythm as well as with atrial pacing

Fig 1 presents the variation of the A H interval at progressive concentrations of Dobutamine both without and with atrial pacing Significant

shortening of A H occurs with an infusion rate of 10 μg per kilogram per minute without obvious further changes at a higher infusion rate

Fig 2 emphasizes the influence of atrial pacing on A H conduction time with and without Dobutamine Increasing heart rate from control to 140 per minute is associated with progressive increment in A H conduction time when no drug is used While the administration of Dobutamine at a rate of 5 μg per kilogram per minute fails to influence the prolongation of A H interval induced by atrial pacing concentrations of 10 and 15 μg per kilogram per minute effectively prevent such prolongation

Fig 3 depicts the typical changes observed in one patient with the administration of Dobutamine marked shortening of the A H interval occurs at similar driving rates

H V interval The H V interval did not change significantly during spontaneous rates or with pacing at different concentrations of Dobutamine (with the exception of the third concentration of 15 μg per kilogram per minute during spontaneous rhythm)

Discussion

Catecholamines are thought to influence A V conduction in man Objective demonstration of this property has been particularly shown for isoproterenol Wallace and Sarnoff[8] demonstrated that sympathetic nerve stimulation in animals caused significant changes in A V conduction the A H interval was markedly shortened with no effect upon intraventricular conduction (H V interval) Damato and co workers using the His bundle recording technique in man demonstrated that isoproterenol shortens the A H interval without affecting the H V interval Dhingra and co workers not only found shortening in the A H interval but observed facilitation of conduction in the His Purkinje system with administration of isoproterenol

Our study with Dobutamine demonstrates a clear facilitation of A V conduction as depicted in Fig 1 The initial concentration of 5 μg per kilogram per minute did not induce significant changes in the A H interval either during spontaneous rhythm or with atrial pacing however infusion rates of 10 and 15 μg per kilogram per minute shortened the A H interval significantly in comparison with control values Fig 2 presents the data in a different way progressive lengthening of the A H interval takes place as the rate increases which is a well known phenomenon already described[7] The initial concentration of 5 μg per kilogram per minute did not modify such response However Dobutamine at infusion rates of 10 and 15 μg per kilogram per minute kept the A H interval practically unchanged despite the increasing pacing rate This again demonstrates the enhancement of A V conduction produced by the drug

Changes in the H V interval with Dobutamine were small and practically of no statistical significance

No consistent changes could be observed for intra atrial conduction times It is conceivable that shortening of such intervals might take place but further investigation of this aspect would require obtainment of multiple and simultaneous intra atrial recordings not performed in this study

From available data Dobutamine acts as a positive inotropic agent like isoproterenol but with less increase in heart rate and with no induction of arrhythmias

This property coupled with facilitation of A V conduction could make of Dobutamine a useful agent in the management of patients with the combination of heart failure and spontaneous or induced A V conduction abnormalities

Summary

Dobutamine a new beta stimulating catecholamine has been investigated in terms of its effect upon atrioventricular conduction

Bundle of His recordings were obtained on six patients in basal conditions and with right atrial pacing at rates of 100 120 and 140 per minute Recordings were repeated following intravenous administration of Dobutamine in doses of 5 10 and 15 μg per kilogram per minute Dose response curves were thus obtained for A H and H V intervals

Heart rate increased only moderately with progressive concentrations of the drug Very significant facilitation of A H conduction was demonstrated with doses of 10 and 15 μg per kilogram per minute with no effect upon H V times

Dobutamine may be a clinically useful inotropic agent in conditions associated with A V conduction disturbances

We are grateful to Eli Lilly Research Laboratories for making Dobutamine available to us for this investigation

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Reversibility of left ventricular asynergy by nitroglycerin in coronary artery disease

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In 1967 Herman Klein and Gorlin and their co workers described the use of left ventriculography to assess regional disorders of wall motion in patients with coronary artery disease These and subsequent studies have demonstrated that localized myocardial asynergy is frequently found in patients thought to have scar formation on the basis of prior documented myocardial infarction[4,5] These same motion abnormalities may also be noted however in patients without prior myocardial infarction who have no scar on histological examination[3] Reversibility of abnormal contractile patterns in the latter group following revascularization surgery would suggest a functional disorder presumably ischemia as the etiology of disordered motion[6] It would be advantageous to have a simple yet reliable method to distinguish anatomic from functional causes of left ventricular asynergy since this distinction assumes critical importance when considering patients for coronary artery surgery The purpose of this report is to relate our experience with the use of a well known antianginal drug nitroglycerin in assessing the reversibility of myocardial asynergy as defined by left ventriculography in patients with coronary artery disease

Materials and methods

Thirty six patients undergoing routine cardiac catheterization for evaluation of coronary artery disease were the subjects for this study Informed consent was obtained from all patients participating in the study Six patients had no organic heart disease The remaining 30 had significant coronary artery disease involving one or more vessels Of these 30 seven had proved transmural myocardial infarction in the past with diagnostic electrocardiographic QRS changes in the other twenty three neither historical nor electrocardiographic (ECG) evidence of myocardial infarction could be obtained

Left ventricular cineangiography at 64 fr per second was performed in the 30 degree RAO projection with 45 c c of solution containing 66 per cent meglumine diatrizoate and 10 per cent sodium diatrizoate (Renografin 76) To 32 patients 0 4 mg of sublingual nitroglycerin was given 4 minutes after the first angiogram When the hemodynamic effects of nitroglycerin were noted as evidenced by a fall in left ventricular end diastolic pressure (LVEDP) and/or arterial blood pressure and/or an increase in heart rate a second left ventricular angiogram was performed with the same position and tube height (usually 8 minutes after the first angiogram) (Table I) In the remaining four patients the second angiogram was performed 8 minutes after the first

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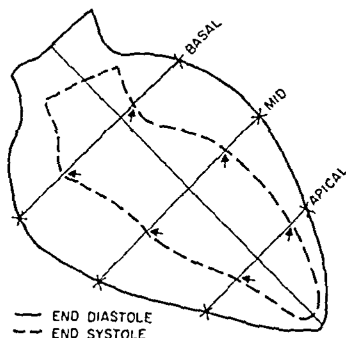


Fig 1 Method of obtaining percentage of systolic shortening (PSS) by superimposition of end diastolic and end systolic frames The longitudinal end diastolic axis was drawn from the mid point of the aortic valve plane to the apex and divided into four equal segments by three minor chords labeled basal mid and apical The end diastolic length of each minor chord was measured between the points indicated by × and the end systolic length between the points indicated by arrows

angiogram without the intervening administration of sublingual nitroglycerin Subsequent to left ventricular angiography, all patients underwent selective coronary cinearteriography

Each angiogram was evaluated both qualitatively and semiquantitatively An outline of the left ventricular cavity was traced during end diastole and end systole the individual frames were superimposed (Fig 1) Only cycles occurring during consecutive beats of sinus rhythm were selected for analysis Relative volumes were derived by means of the area length method of Sandler and Dodge and ejection fraction (EF) was calculated from these relative measurements Three minor chords—basal, mid, and apical—were drawn perpendicular to the longitudinal axis dividing it into four equal segments Percentage systolic shortening (PSS) of each of the three minor chords was calculated from the following formula

$$\frac{\text{End diastolic length} - \text{End systolic length}}{\text{End diastolic length}} \times 100$$

The change in EF and PSS for each chord from the first to the second angiogram was then calculated

The statistical significance of changes within and between patient groups was determined by Student's t test for paired and group means respectively p values of less than 0 05 were regarded as significant

Results

The results of the study were classified as follows

Group 1 Effect of first angiogram on second angiogram (n = 4) To determine the possible effect of the initial angiogram on a subsequent angiogram, four studies were performed in one normal individual and three patients with coronary artery disease who did not have a past myocardial infarction The second left ventriculogram was performed 8 minutes after the first no intervention was employed between the two studies Comparison of both studies revealed no significant changes in either EF or PSS (Table II) We deliberately avoided performing a second angiogram without nitroglycerin intervention in patients with significant asynergy for fear of untoward hemodynamic deterioration However one patient in Group 1 had moderate inferior wall hypokinesis on the first ventriculogram which was not noted during the time of the study He demonstrated no significant change in wall motion pattern during the second angiogram

Effects of nitroglycerin

Group 2 Normal left ventricles (n = 8) (Fig 2) There were a total of eight patients in this group Five had no organic heart disease and three patients had coronary artery disease without previous myocardial infarction or left ventricular asynergy in their first angiogram The three patients with coronary artery disease could not be distinguished qualitatively or quantitatively from the five normal subjects on the basis of either their first angiogram or their response to nitroglycerin Therefore these eight patients served as controls for the effect of nitroglycerin on normal ventricles There were modest but significant increases in EF and PSS of mid and apical chords with nitroglycerin (Table II) There were no significant changes in PSS of the basal segment

Group 3 Myocardial infarction (n = 7) (Fig 3) This group included seven patients with transmural myocardial infarction in the past Six of them had anterior wall and one had diaphrag

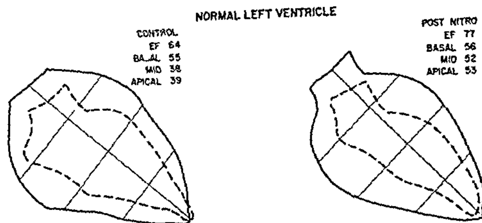


Fig 2 Effect of nitroglycerin on the left ventricular angiogram of a 44 year old female patient with no organic heart disease

Table I Hemodynamic effects of nitroglycerin

	Heart rate (beats/min)		*Systolic pressure (mm Hg)*		*LVEDP (mm. Hg)*	
	Mean	*1 SE*	*Mean*	*1 SE*	*Mean*	*1 SE*
Rest	75.7	2.7	141.4	4.6	13	1.6
Prenitro*	76.9	2.4	148.6	5.4	21	1.7
Postnitro†	81.8	2.1	133.8	4.9	9	1.2
P value						
Postnitro vs. prenitro	< 0.005		< 0.001		< 0.001	
Postnitro vs rest	< 0.005		< 0.01		< 0.001	

*Before nitroglycerin, 4 minutes after first angiogram
†After nitroglycerin just prior to second angiogram

matic wall infarction The first left ventricular angiogram showed asynergy in the zones corresponding to the ECG site of infarction There was no significant change in either EF or PSS of the three minor chords following the administration of nitroglycerin (Table II) This response was characterized as irreversible asynergy

Group 4 Asynergy without myocardial infarction Seventeen coronary artery disease patients with asynergy during the initial ventriculogram but without previous myocardial infarction were included in this group They were further subdivided into three groups depending upon their response to nitroglycerin

Group 4A Irreversible asynergy (n = 4) (Fig 4) There were four patients in this group Two of them presented with chest pain one atypical and the other typical of angina pectoris The other two presented with congestive heart failure They all had severe diffuse coronary artery disease including at least two major vessels They exhibited diffuse hypokinesis rather than discrete segmental dysfunction Similar to the myocardial infarction group there was no significant change of either EF or PSS in response to nitroglycerin (Table II)

Group 4B Partially reversible asynergy (n = 5) (Fig 5) This group included five patients who demonstrated mild left ventricular asynergy in their first angiogram The changes in EF and PSS produced by nitroglycerin were similar to the values in normal subjects however both resting and postnitroglycerin angiograms showed borderline subnormal values for these parameters Qualitatively it was difficult to identify a discrete asynergic area in either ventriculogram

Group 4C Completely reversible asynergy (n = 8) (Figs 6A and 6B) This group consisted of eight patients who demonstrated moderate to severe asynergy on their first ventriculogram In contrast to Group 4B discrete asynergic zones could easily be identified by inspection Two

Table II Percentage of systolic shortening

	Basal			Mid			Apical	
	Control	Postnitro	P value	Control	Postnitro	P value	Control	Postnitro
1 Control† (n = 4)	41 ± 1 8‡	43 ± 5 2	> 0 5	41 ± 4 3	35 ± 4 8	> 0 1	47 ± 9 2	57 ± 6 8
2 Normal ventricles (n = 8)	45 ± 2 9	45 ± 3 0	> 0 5	39 ± 2 6	50 ± 1 8	< 0 005	53 ± 5 5	71 ± 5 4
3 Myocardial infarction (n = 7)	28 ± 4 0	29 ± 1 3	> 0 5	20 ± 2 9	21 ± 3 0	> 0 5	23 ± 6 4	24 ± 6 3
4 Asynergy without myocardial infarction								
A Irreversible (n = 4)	22 ± 9 0	23 ± 10 5	> 0 4	16 ± 7 9	18 ± 8 1	> 0 5	14 ± 7 2	16 ± 7 7
B Partially reversible (n = 5)	29 ± 2 4	31 ± 1 7	> 0 05	31 ± 3 0	40 ± 2 7	< 0 001	49 ± 4 5	64 ± 3 8
C Completely reversible (n = 8)	35 ± 3 4	40 ± 3 0	> 0 4	22 ± 2 6	51 ± 3 6	< 0 001	30 ± 4 6	73 ± 2 1

P values are estimated for change from control to postnitro or second angiogram without intervention as the case may be
†For Group 1 postnitro signifies second angiogram without intervening nitroglycerin
‡± = 1 SE

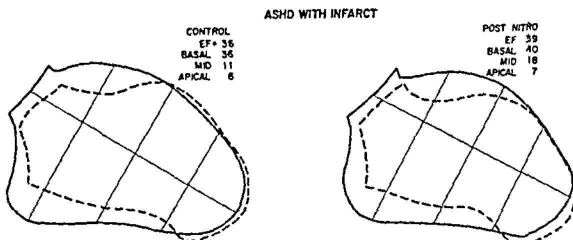


Fig 3 Effect of nitroglycerin on the left ventriculogram of a 40 year old man with previous anterior wall myocardial infarction

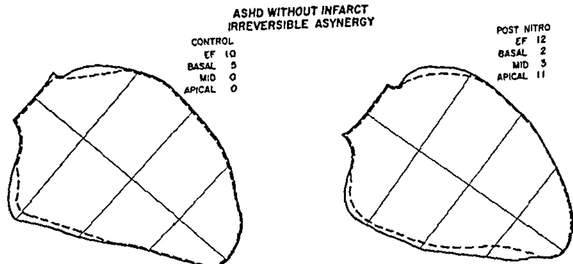


Fig 4 Effect of nitroglycerin on a 64 year old man who presented with symptomatic congestive heart failure and chest pain He did not have historical or ECG evidence of myocardial infarction

	Ejection fraction (%)		
P value	*Control*	*Postnitro*	*P value*
> 0 2	68 ± 3 2	68 ± 2 7	> 0 5
< 0 05	69 ± 2 2	76 ± 2 1	< 0 0?5
> 0.5	42 ± 5.2	47 ± 4 9	> 0 05
> 0 5	36 ± 12 7	38 ± 11 2	> 0 2
< 0 001	58 ± 4 1	69 ± 2 4	< 0 0?5
< 0 001	5? ± 4 1	73 ± 2 5	< 0 001

patients experienced angina around the time of the study one immediately after and one during the initial left ventriculogram The changes in EF and PSS induced by nitroglycerin were significantly greater than those exhibited by Groups 2 or 4B The exaggerated response did not include the basal segment whose PSS was rarely abnormal in the resting state Although PSS and EF were significantly less than normal in the control angiograms of this group values for post nitroglycerin left ventriculograms were similar to those of normal subjects In this group reversal of asynergy was complete

Heart rate arterial pressure and LVEDP response to nitroglycerin were similar in all groups the changes in these parameters are compatible with significant drug effect

There was no evident correlation between the extent of coronary collateralization and the response to nitroglycerin but the numbers in each group were too small to draw meaningful conclusions

Discussion

When selecting patients for myocardial revascularization procedures evidence must be obtained that tissue viability is maintained in the area where coronary blood flow is to be augmented In clinical practice this determination is usually made by correlating the ECG with left ventriculography performed in the resting state Asynergic areas corresponding to an ECG site of transmural infarction are generally assumed to represent myocardial scars which are metabolically inert and therefore incapable of producing ischemic pain[10 11] When documentation of prior myocardial infarction is not available however the meaning of asynergic zones is conjectural. The studies of Gorlin Klein and Sullivan[3] have demonstrated the variable histologic picture associated with specific patterns of asynergy Pasternac and associates[12] and Dwyer have shown that asynergy may be produced or worsened by an acute ischemic stress such as atrial pacing attesting to the dynamic status of wall motion abnormalities Of clinical importance however is the reversibility of abnormal ventricular motion

The potential for reversibility of myocardial asynergy has recently been assessed by means of left ventriculographic techniques in combination with catecholamine infusion[15] or induction of post-extra systolic potentiation[1] Both of these methods should increase contractility participation of the previously asynergic zone in this augmentation of contractility suggests reversibility Using the former method Horn and associates[5] reported improvement in nine of 13 patients with resting asynergy while Dyke and associates using post-extra systolic potentiation noted normalization of axis shortening in seven of 17 patients with previously hypokinetic areas Since both of these interventions increase contractility a judicious balance must be struck between increased myocardial oxygen demands created by the intervention and the available blood supply If the intervention produces a greater disparity between oxygen supply and demand than that existing at rest paradoxical exacerbation of asynergy may result Horn and associates reported worsening of asynergy in two patients during epinephrine ventriculography Although Dyke and associates did not find exacerbation of asynergy in 15 patients post-extra systolic potentiation is a relatively complex procedure requiring the use of a specialized pacemaker unit

Nitroglycerin on the other hand is known to be a relatively safe easily administered pharmacologic agent which will reverse both the hemodynamic and metabolic abnormalities induced by acute myocardial ischemia[1 4] This reversal may result primarily from decreases in ventricular pre

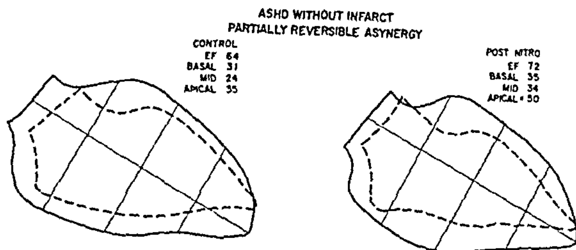


Fig 5 A 5? year old woman with angina but no previous myocardial infarction Note the mild resting asynergy without discrete zone of abnormal motion which improves with nitroglycerin

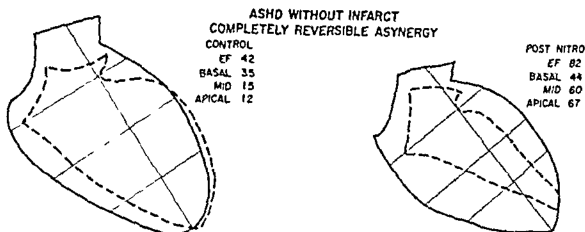


Fig 6A A ?4 year old man with angina but no previous myocardial infarction There is evident asynergy of the anterior wall in the control ventriculogram nitroglycerin completely abolishes this asynergy

and after load[19] and/or a redistribution of coronary blood flow[2] [3] Although the former appears to be the more important mechanism the question has not been conclusively settled In any case this drug appeared to be a useful agent which might acutely reverse abnormalities of left ventricular motion due to a functional process viz ischemia by creating a more favorable balance between myocardial oxygen require ments and delivery It would not have the disad vantage of the above two methods It is of interest that no instance of new or increased asynergy was noted in the present study

In patients with coronary artery disease but no evidence of myocardial infarction three different responses to nitroglycerin were noted Similar to the myocardial infarction group four of these patients (Group 4A) failed to show improvement in left ventricular contraction patterns following the administration of nitroglycerin In contrast to the infarction group however they tended to have diffuse rather than discrete zones of asynergy and to have more extensive coronary arterial disease Since three of the four failed to manifest clinical criteria for the diagnosis of atherosclerotic heart disease they resembled the description by Burch Tsui, and Harb[22] of patients with ischemic cardiomyopathy It is of interest that extensive fibrotic replacement of the myocardium was found at autopsy in Burch s two patients The basis for asynergy in our patients can be only speculative but it would appear likely that actual replacement of contractile elements underlies the lack of response to nitro glycerin in the infarction and irreversible asyner gy group It is unlikely that such patients will be benefited by revascularization surgery[23]

The complete reversal of asynergy (Group 4C) in eight subjects suggests a functional process probably ischemia as the basis for resting myocardial asynergy Successful revasculariza tion of these patients would probably prove bene

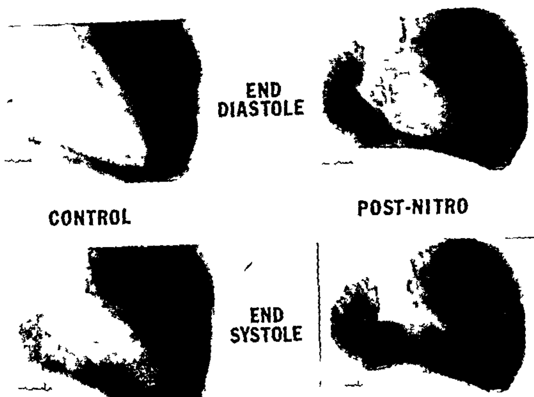


Fig 6B Cine frames corresponding to Fig 6A

ficial Although five other patients (Group 4B) showed normal changes following nitroglycerin they continued to manifest subnormal absolute values for EF and PSS It is not possible to state whether the ba is for this response is functional or anatomic in origin

It is possible that undetected myocardial infarction occurred in groups other than Group 3 This especially applies to Group 4A If only patients with discrete left ventricular asynergy are considered however it is significant that all patients with completely reversible asynergy did not have ECG or historical evidence of myocardial infarction whereas those with irreversible asynergy all met ECG criteria for transmural infarction It appears unlikely that complete reversibility of discrete asynergic zones would occur in the presence of undetectable transmural myocardial infarction

The present study corroborates the findings of Helfant and associates[2] who found that the administration of nitroglycerin to patients with coronary artery disease may lead to reversal of left ventricular asynergy as defined by left ventriculography Our study concludes that such changes are most likely to occur in patients with focal asynergy who have not had previous transmural myocardial infarction In patients with transmural infarction or ischemic cardiomyopathy characterized by diffuse hypokinesis such changes are unlikely to occur

Summary

To evaluate the potential reversibility of left ventricular asynergy in patients with coronary artery disease pre and postnitroglycerin left ventriculography was performed in 32 subjects In four other subjects left ventriculography was repeated without intervention of nitroglycerin Changes in ejection fraction and percentage of systolic shortening of three minor axes from the first to the second angiogram were then calculated Changes were not significant for the myocardial infarction group or for the control group without the intervention of nitroglycerin Normal left ventricles showed small but significant changes ($p < 0.05$) Patients with coronary artery disease but without previous myocardial infarction who demonstrated asynergy in their first angiogram showed three types of response (1) no significant change ($p > 0.05$)—irreversible asynergy (2) significant change ($p < 0.025$) with

residual dysfunction—partially reversible asynergy, (3) significant change ($p < 0.001$) without residual dysfunction—completely reversible asynergy. It is concluded that postnitroglycerin ventriculography is useful in assessing the reversibility of left ventricular asynergy in patients with coronary artery disease.

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Effects of intravenous verapamil on cardiac arrhythmias and on the electrocardiogram

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Numerous compounds of varying potencies are now available for the control of clinical and experimental cardiac arrhythmias Many of the new agents such as beta adrenergic receptor blocking drugs and amiodarone[3] have anti anginal as well as antiarrhythmic properties Another such compound is verapamil whose antiarrhythmic action appears to be markedly different from that of other compounds[1] It was originally considered to be a potent coronary dilator[5] and was subsequently found to be effec tive in the treatment of angina pectoris[6] Its antiarrhythmic actions, well demonstrated in experimental animals[7 9] have recently been confirmed in a number of preliminary clinical studies although its complete spectrum of therapeutic use remains to be fully evaluated

The exact mechanism of action of verapamil is also not completely understood However the drug has aroused great interest because of the possibility that its salutary effects in arrhythmias may be related to the property of specifically and selectively inhibiting depolarizing calcium cur rents in the heart In this report we present the results of our studies of its effect after intra venous administration on a variety of cardiac tachyarrhythmias and on the electrocardiogram in patients with sinus rhythm

Methods

The data on which this report is based were derived from 59 patients who were given intra venous verapamil (Cordilox Isoptin Knoll AG Ludwigshafen West Germany) after informed consent Two groups of patients were studied

The first series consisted of 15 patients in sinus rhythm who underwent diagnostic cardiac cathe terization for the evaluation of ischemic or valvular heart disease Hemodynamic and elec trocardiographic effects of intravenous verapamil were studied after the conclusion of the diag nostic and angiographic procedures The results of the hemodynamic measurements are reported elsewhere[23] There were 14 males and 1 female in this group their ages ranged between 20 and 57 years Nine patients had ischemic heart disease 4 had rheumatic valvular lesions, and 2 were found to have no significant organic cardiac disease After diagnostic catheterization each patient rested for 20 minutes for stabilization of hemody namic functions Base line electrocardiogram (ECG) and hemodynamic measurements were recorded at a paper speed of 50 mm per second and 200 mm per second with an Electronics for Medicine DR 8 photographic recorder Verapamil (10 mg) was then given intravenously over a period of 2 minutes Complete sets of data were obtained between 3 and 5 minutes 10 minutes and 20 minutes after the completion of adminis

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Fig 1 Serial records of the electrocardiogram in Patient No 4 (Table II) with SVT (167/min) given 10 mg of verapamil intravenously Note the development of A V dissociation with slowing of the ventricular rate at 1 minute after verapamil was given atrial fibrillation supervened at 2 minutes and reversion to stable sinus rhythm occurred at 5 minutes after the drug was administered

Table I Effects of intravenous verapamil on the electrocardiogram in patients with sinus rhythm

Interval (msec)	*Before verapamil*	*After verapamil*	*n*	*Significance*
R R	743 ± 38	738 ± 27	15	NS
P R	180 1 ± 6 2	205 4 ± 8 1	13	p < 0 001
QRS	65 5 ± 4 1	66 1 ± 4 6	13	NS
Q T	437 8 ± 9 9	451 0 ± 6 6	12	NS

Abbreviations msec = milliseconds *n* = number of patients NS = not significant

tration of the drug The ECG was analyzed for changes in R R, P R QRS and Q T intervals At least five ECG complexes were analyzed in order to obtain the mean value for each parameter which was measured

The second group was comprised of 44 patients with cardiac tachyarrhythmias treated with intravenous verapamil before other antiarrhythmic agents were used In this group there were 26 males and 18 females their ages ranged between 2 and 76 years At the time that verapamil was administered, 27 patients in this series were on digitalis as chronic medication

In adults, up to 10 mg of verapamil was given In children, the dose was adjusted according to weight Blood pressure and control ECG were recorded before verapamil was given intravenously over 60 seconds and the ECG was monitored continuously during the entire period of injection Whenever possible, blood pressure and ECG were recorded at 1, 5 10, and 30 minutes after the injection of the drug Some patients in this group had more than one episode of arrhythmia treated with verapamil Three patients were treated for more than one type of arrhythmia one patient successively for supraventricular tachycardia (SVT) atrial flutter, and atrial fibrillation another patient for SVT and atrial fibrillation, and a third patient for SVT and atrial flutter For the purposes of analysis these 3 patients are grouped separately for each type of arrhythmia Throughout the study, the rhythm recorded 30 minutes after the injection of verapamil was arbitrarily considered to be the end result of the drug action

Results

Effects of verapamil on ECG In the group of patients with sinus rhythm because of technically unsatisfactory tracings it was not possible to measure accurately the P R interval in one patient the QRS duration in another, and the Q T interval in two others One patient developed junctional rhythm shortly after verapamil was

Table II Effects of intravenous verapamil on supraventricular tachycardia

Patient No	Age (yr)	Diagnosis	Previous therapy	Before verapamil HR/min	Before verapamil BP (mm Hg)	After verapamil HR/min	After verapamil BP (mm Hg)	Dose (mg)	Outcome
1	63	IDH with acute MI	Digoxin Procainamide	172	100/80	72	8./60	10	SR
2	38	Idiopathic SVT	None	165	–	110	–	2.5	SR
3	67	IHD with acute MI	None	270	–	110	–	10	SR
4	26	RHD (postop)	Digoxin	169	100/80	100	100/80	10	SR
5	64	IHD with acute MI	None	145	110/90	90	1?0/65	10	SR
6	39	RHD (postop)	Digoxin	186	–	95	–	10	SR
7	51	RHD	None	155	110/70	80	110/70	10	SR
8	45	IHD	Digoxin	136	–	105	–	5	SR
9	51	Idiopathic SVT	None	134	1?0/70	86	115/85	10	SR
10	6	VSD	None	230	85/65	136	110/80	3.5	SR
11	9	Ebstein's anomaly	None	150	100/70	125	100/70	5	SR (3 episodes)
12	46	Idiopathic SVT	None	200	Unrecordable	84	90/-	10	SR
13(a)	16	RHD	Digoxin	165	120/90	72	100/70	10	SR (2 episodes)
(b)	16	RHD	Digoxin	165	–	80	–	10	A V dissociation (2 episodes, both resulting in SR 1 hr later)
14	12	RHD (postop)	Digoxin	214	–	145	–	5	A V dissociation with JR
15	?6	IHD with acute MI	Digoxin	13?	110/90	7?	100/70	10	A V dissociation then SR 2 hr later
16	3?	RHD	Digoxin quinidine	112	100/70	65	70/50	10	A V block increased from 2 1 to 4 1
17	2	WPW syndrome	None	?60	–	235	–	3.5	Unchanged

Abbreviations IHD = ischemic heart disease MI = myocardial infarction HR = heart rate BP = blood pressure SVT = supraventricular tachycardia RHD = rheumatic heart disease postop = postoperative VSD = ventricular septal defect WPW = Wolff Parkinson White SR = sinus rhythm A V = atrioventricular JR = junctional rhythm

given and P R QRS and Q T intervals could not be determined The mean results for the other patients analyzed for significance by Students t test for paired data are presented in Table I The peak effects of the drug usually manifest at 5 to 10 minutes after its administration have been compared with the control values No significant changes were found with respect to the R R QRS and Q T intervals The P R interval however increased after verapamil in all patients The mean change from 186 ± 6 msec (mean ± S E M) to 205 ± 8 msec was highly significant ($p < 0.001$)

Effects of verapamil on cardiac arrhythmias The effects of verapamil on the different types of arrhythmias and the associated features are summarized in Tables II through V

Supraventricular tachycardia The effects of verapamil in 17 patients with SVT are shown in Table II Recognized cardiac disease was present in all cases except in 3 patients who had no clinical radiologic or electrocardiographic evidence of heart disease after the paroxysmal arrhythmia was corrected Intravenous verapamil restored sinus rhythm in 12 of the 17 patients (Nos 1 12 in Table II) In one of these patients reversion to sinus rhythm was preceded by transient A V dissociation in another A V dissociation and atrial fibrillation developed but sinus rhythm was established at 5 minutes after administration of verapamil This sequence is shown in Fig 1

One patient (No 13) was given verapamil for four separate episodes of SVT on two occasions



Fig 1 Serial records of the electrocardiogram in Patient No 4 (Table II) with SVT (167/min) given 10 mg of verapamil intravenously Note the development of A V dissociation with slowing of the ventricular rate at 1 minute after verapamil was given atrial fibrillation supervened at 2 minutes and reversion to stable sinus rhythm occurred at 5 minutes after the drug was administered

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Interval (msec)	*Before verapamil*	*After verapamil*	*n*	*Significance*
R R	743 ± 38	738 ± 27	15	NS
P R	186.1 ± 6.2	205.4 ± 8.1	13	$p < 0.001$
QRS	65.5 ± 4.1	66.1 ± 4.6	13	NS
Q T	457.8 ± 9.9	451.0 ± 6.6	12	NS

Abbreviations msec = milliseconds n = number of patients NS = not significant

tration of the drug The ECG was analyzed for changes in R-R P R QRS and Q T intervals At least five ECG complexes were analyzed in order to obtain the mean value for each parameter which was measured

The second group was comprised of 44 patients with cardiac tachyarrhythmias treated with intravenous verapamil before other antiarrhythmic agents were used In this group there were 26 males and 18 females, their ages ranged between 2 and 76 years At the time that verapamil was administered, 27 patients in this series were on digitalis as chronic medication

In adults, up to 10 mg of verapamil was given In children the dose was adjusted according to weight Blood pressure and control ECG were recorded before verapamil was given intravenously over 60 seconds and the ECG was monitored continuously during the entire period of injection Whenever possible blood pressure and ECG were recorded at 1, 5 10 and 30 minutes after the injection of the drug Some patients in this group had more than one episode of arrhythmia treated with verapamil Three patients were treated for more than one type of arrhythmia one patient successively for supraventricular tachycardia (SVT) atrial flutter and atrial fibrillation, another patient for SVT and atrial fibrillation and a third patient for SVT and atrial flutter For the purposes of analysis these 3 patients are grouped separately for each type of arrhythmia Throughout the study, the rhythm recorded 30 minutes after the injection of verapamil was arbitrarily considered to be the end result of the drug action

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Patient No	Age (yr)	Diagnosis	Previous therapy	Before verapamil		After verapamil		Dose (mg)	Outcome
				HR/min	BP (mm Hg)	HR/min	BP (mm Hg)		
1	63	IHD with acute MI	Digoxin Procainamide	1??	100/80	72	85/60	10	SR
2	38	Idiopathic SVT	None	165	–	110	–	2 5	SR
3	67	IHD with acute MI	None	220	–	110	–	10	SR
4	?6	RHD (postop)	Digoxin	169	100/80	100	100/80	10	SR
5	64	IHD with acute MI	None	14?	110/90	90	1?0/6?	10	SR
6	39	RHD (postop)	Digoxin	186	–	95	–	10	SR
7	51	RHD	None	155	110/70	80	110/70	10	SR
8	4?	IHD	Digoxin	136	–	105	–	5	SR
9	51	Idiopathic SVT	None	134	1?0/?0	86	115/85	10	SR
10	6	VSD	None	?30	85/65	136	110/80	3 5	SR
11	9	Ebstein s anomaly	None	150	100/ 0	125	100/70	5	SR (3 episodes)
12	46	Idiopathic SVT	None	200	Unrecordable	84	90/-	10	SR
13(a)	16	RHD	Digoxin	165	1?0/90	7?	100/?0	10	SR (2 episodes)
(b)	16	RHD	Digoxin	165	–	80	–	10	A V dissociation (? episodes, both resulting in SR 1 hr later)
14	12	RHD (postop)	Digoxin	214	–	145	–	5	A V dissociation with JR
15	76	IHD with acute MI	Digoxin	136	110/90	75	100/?0	10	A V dissociation then SR 2 hr later
16	?2	RHD	Digoxin quinidine	112	100/?0	6?	?0/50	10	A V block increased from 2 1 to 4 1
17	2	WPW syndrome	None	260	–	235	–	3 ?	Unchanged

Abbreviations IHD = ischemic heart disease MI = myocardial infarction HR = heart rate BP = blood pressure SVT = supraventricular tachycardia RHD = rheumatic heart disease postop = postoperative VSD = ventricular septal defect WPW = Wolff Parkinson White SR = sinus rhythm A V = atrioventricular JR = junctional rhythm

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One patient (No 13) was given verapamil for four separate episodes of SVT on two occasions

Table III Effects of intravenous verapamil on atrial flutter

Patient No	Age (yrs)	Diagnosis	Previous therapy	Before verapamil HR/min	Before verapamil BP (mm Hg)	After verapamil HR/min	After verapamil BP (mm Hg)	Dose (mg)	Outcome
1	16	RHD (postop)	Isoprenaline infusion	143	–	76	–	10	Flutter with increased second degree A V block
2	65	Gastrectomy (?) IHD	None	174	–	94	–	7	Flutter with increased second degree A V block
3	63	IHD with acute MI	Digoxin procainamide	140	100/80	83	65/50	10	Flutter with increased second degree A V block
4	50	IHD (postop)	Digoxin	180	–	86	–	10	Flutter with increased second degree A V block
5	26	RHD	Digoxin	190	90/65	45	80/50	10	Flutter with increased second degree A V block
6	52	IHD with acute MI	Digoxin	160	90/60	108	105/80	10	Flutter with increased second degree A V block (3 episodes)
7	51	IHD (postop)	Digoxin Procainamide	160	105/80	85	110/80	10	AF
8	65	RHD	Diuretic	150	140/100	130	110/70	10	AF
9(a)	70	IHD	None	165	110/90	83	100/80	10	AF
(b)	70	IHD	Digoxin	114	–	70	–	10	SR
10(a)	62	IHD with acute MI	Digoxin	133	110/90	104	110/85	10	AF
(b)	62	IHD with acute MI	Digoxin	161	100/80	88	85/65	10	SR
11	51	IHD	Digoxin	78	–	78	–	10	Unchanged

Abbreviations IHD = ischemic heart disease MI = myocardial infarction HR = heart rate BP = blood pressure AF = atrial fibrillation SR = sinus rhythm A V = atrioventricular RHD = rheumatic heart disease postop = postoperative

sinus rhythm was restored promptly, but during the other two episodes A V dissociation with junctional rhythm resulted after administration of verapamil However sinus rhythm developed in both instances 1 hour later A V dissociation was also the end result (i e at 30 minutes after drug administration) in two other patients (Nos 14 and 15) with one of these (No 15) reverting to sinus rhythm at 2 hours One patient (No 16) had SVT with 2 1 A V conduction, after administration of verapamil, the block increased to 4 1 A V conduction but sinus rhythm was not achieved The rhythm remained unresponsive to verapamil in Patient No 17, who had SVT due to the Wolff Parkinson White syndrome He was subsequently treated with direct current cardioversion

When verapamil was effective in controlling SVT, the reversion was prompt, usually within minutes of intravenous injection A typical response is shown in Fig 2 Of the 13 patients (Nos 1 13) with SVT who responded to verapamil 11 had reversion to sinus rhythm within 5 minutes of administration of the drug In some patients, a mild but transient fall in blood pressure occurred after verapamil was given but the usual response was the correction of hypotension with the control of the arrhythmia, the effect being particularly marked in patients with rapid heart rates (Fig 3)

Atrial flutter The responses in 11 patients with atrial flutter given verapamil are shown in Table III Before verapamil was given the rhythm was

Table IV Effects of intravenous verapamil on atrial fibrillation

Patient No	Age (yrs)	Diagnosis	Previous therapy	Before verapamil		After verapamil		Dose (mg)	Outcome
				HR/min	BP (mm Hg)	HR/min	BP (mm Hg)		
1	61	IHD	None	188	190/110	150	160/100	10	AF with ventricular slowing (2 episodes)
2	63	IHD with acute MI	Digoxin	168	100/70	139	90/65	5	AF with ventricular slowing (2 episodes)
3	56	Hypertension	None	1?0	180/110	102	80/50	5	AF with ventricular slowing
4	53	RHD (postop)	Digoxin	166	1?0/75	95	100/60	10	AF with ventricular slowing
5	61	Hypertension Ca lung	Digoxin	1?0	150/90	113	135/80	10	AF with ventricular slowing (2 episodes)
6	56	IHSS (postop)	None	186	105/70	131	110/75	10	AF with ventricular slowing
7	50	Idiopathic AF	None	15?	1?0/100	136	105/80	10	AF with ventricular slowing
8	54	IHD with acute MI	Propranolol	110	115/80	81	100/65	10	AF with ventricular slowing
9	55	RHD	Digoxin	1?4	–	136	–	10	AF with ventricular slowing
10	45	RHD	Digoxin	1?0	100/?0	?6	90/60	10	AF with ventricular slowing
11	21	Idiopathic AF	None	116	90/65	72	9?/?0	10	AF with ventricular slowing
12	26	RHD	Digoxin	1?5	1?5/6?	92	100/?0	10	Sinus rhythm

Abbreviations IHD = ischemic heart disease MI = myocardial infarction HR = heart rate BP = blood pressure AF = atrial fibrillation SR = sinus rhythm RHD = rheumatic heart disease Ca = carcinoma IHSS = idiopathic hypertrophic subaortic stenosis

Table V Effects of intravenous verapamil on ventricular tachycardia

Patient No	Age (yrs)	Diagnosis	Previous therapy	Before verapamil		After verapamil		Dose (mg)	Outcome
				HR/min	BP (mm Hg)	HR/min	BP (mm Hg)		
1	6?	IHD with acute MI	Procainamide	160	1?0/?5	96	80/50	10	SR
?	5?	IHD with acute MI	Propranolol	125	110/80	125	70/60	10	Unchanged
3	51	IHD with acute MI	Digoxin procainamide	158	–	1?8	–	10	Unchanged
4	?3	IHD with acute MI	None	144	90/–	144	??/–	10	Unchanged
5	5?	IHD LV aneurysm	Digoxin procainamide	159	10?/80	159	80/60	10	Unchanged

Abbreviations IHD = ischemic heart disease MI = myocardial infarction HR = heart rate BP = blood pressure SR = sinus rhythm LV = left ventricular

atrial flutter with 2 1 A V conduction in 9 patients 1 1 A V conduction in 1 patient (No 5) and 4 1 A V conduction in 1 patient (No 11) The immediate effect of verapamil on atrial flutter was extremely consistent With the exception of the patient with 4 1 A V conduction all patients in this group responded with an increase in A V block that resulted in a reduction in ventricular rate (Fig 4) At 5 minutes after injection of verapamil most patients showed unstable A V conduction with the degree of block varying from 2 1 to 5 1 Compared with the mean control rate the mean ventricular rate after verapamil was reduced by 40 per cent ($p < 0.005$) After 30 minutes the end result in 6 patients (Nos 1 6) was persistent atrial flutter with increased A V block, and atrial fibrillation in 3 patients (Nos 7 9) Atrial fibrillation followed by sinus rhythm was the end result of two separate episodes in each of 2 patients (Nos 9 and 10) In both of the

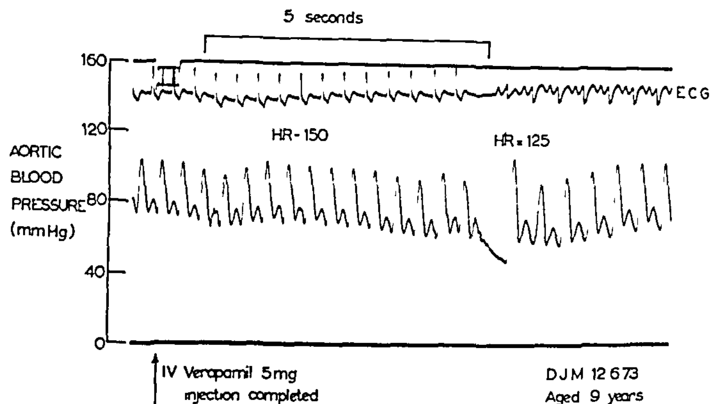


Fig 2 Effect of intravenous verapamil in Patient No 11 (Table II) who developed SVT during cardiac catheterization Reversion to sinus rhythm occurred 5 seconds after completion of injection of verapamil the restoration of sinus rhythm was preceded by transient asystole Note the absence of effect on arterial pressure

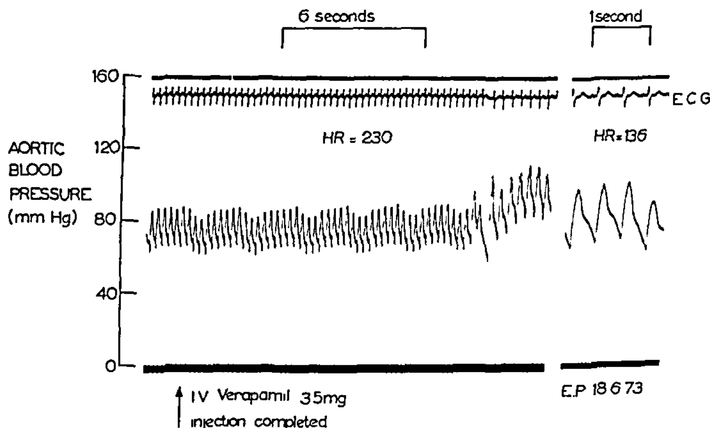


Fig 3 Effect of verapamil on arterial pressure during conversion by the drug of rapid SVT (230/min) to sinus rhythm (136/min) in Patient No 10 (Table II) during cardiac catheterization Note the prompt response of the arrhythmia to verapamil and the accompanying improvement in blood pressure

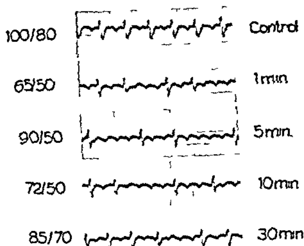


Fig 4 Effects of intravenous verapamil in Patient No 3 (Table III) with atrial flutter with 2 1 A V conduction ventricular rate 140/min (control tracing) After verapamil there is increased A V block reduction in ventricular rate and a fall in blood pressure The maximal A V block occurred between 5 and 10 minutes after injection of 10 mg of verapamil the ventricular rate at 10 minutes was 83/min By 30 minutes the ventricular rate had increased to about 120/min

episodes in which sinus mechanism was restored by verapamil the reversion to normal rhythm was preceded by atrial fibrillation (see Fig 5) In the final patient (No 11) who had atrial flutter with 4 1 A V block before verapamil was given the rhythm was not affected by the drug

Measurement of the F F intervals revealed no change in flutter rate in any patient after administration of verapamil In most patients with atrial flutter verapamil produced a mild to moderate reduction in blood pressure but no other side effects were noted

Atrial fibrillation In patients with atrial fibrillation with a rapid ventricular rate the immediate response to intravenous verapamil was a significant reduction in rate without a change in rhythm in all cases (Table IV) The maximal reduction in rate usually occurred at 5 minutes (Fig 6) at which time the mean ventricular rate for the whole group (n = 12) was 68 per cent of the mean control ventricular rate ($p < 0.005$) Subsequently the rate increased so that the mean ventricular response at 30 minutes for the 11 patients who remained in atrial fibrillation was 78 per cent of the control ($p < 0.005$) In 3 patients regularization of the ventricular rate was observed and a typical example of the

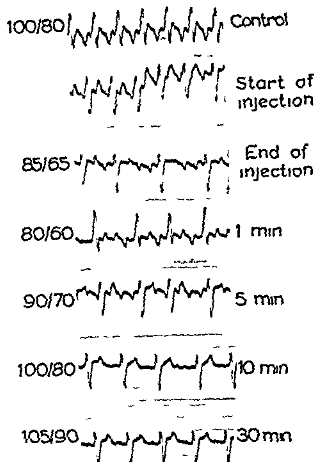


Fig 5 An example of conversion of atrial flutter to sinus rhythm by verapamil in Patient No 10 (Table III) Immediately after administration of verapamil there was enhanced A V block followed by transient atrial fibrillation at 10 minutes after drug injection Sinus rhythm was restored at 30 minutes

phenomenon is illustrated in Fig 7 One of the patients who showed this feature (No 12) subsequently had a reversion to sinus rhythm

It is noteworthy that despite a reduction in ventricular rate in all cases in this group there was a significant fall in blood pressure in 9 patients with little change in 2 patients No other side effects were encountered

Wolff Parkinson White syndrome with atrial fibrillation Three patients in whom atrial fibrillation was associated with the Wolff Parkinson White syndrome were treated with intravenous verapamil There were 2 males and 1 female and one was on digoxin Each patient received 10 mg of verapamil intravenously during continuous electrocardiographic monitoring No change in

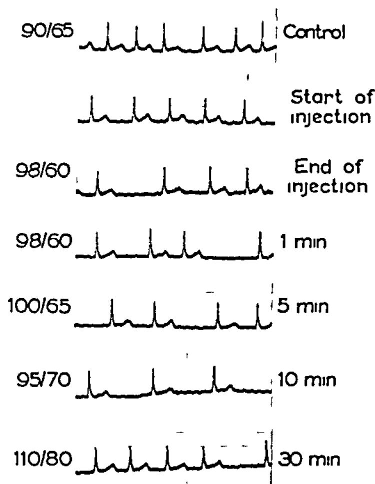


Fig 6 Serial electrocardiographic records illustrating the typical effect of verapamil in a patient (No 11 Table IV) with atrial fibrillation and rapid ventricular rate (116/min) 10 minutes after verapamil was given the ventricular rate was reduced to 72/min and at 30 minutes it was 78/min

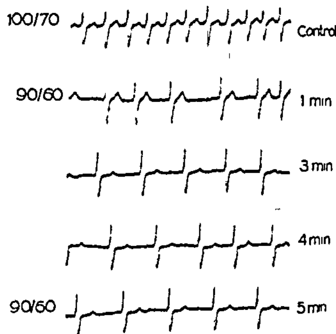


Fig 7 Sequential electrocardiographic tracings demonstrating the regularizing effect of verapamil in Patient No 10 (Table IV) with atrial fibrillation Note the virtually regular slower ventricular response 5 minutes after verapamil was given

rate or rhythm was found during 30 minutes of observation in any of the 3 patients

Ventricular tachycardia Intravenous verapamil was used to treat 5 patients with ventricular tachycardia The clinical features of the patients are shown in Table V Sinus rhythm was restored in only one patient the reversion was associated with transient hypotension A reduction in blood pressure was also found in 3 of the other patients in whom it was recorded before and after the administration of verapamil

Discussion

Verapamil has been shown to have a potent antiarrhythmic effect in many types of experimental arrhythmias[7,10] and initially its action was considered to be similar to that of quinidine[16] However recent studies have revealed that its electrophysiologic actions are strikingly different from those of conventional agents[4,10,15] and can be correlated with the drug s ability to react with superficially located Ca [2] storage sites in myocardial cells,[17] so that during membrane depolarization calcium conductance is selectively inhibited without effect on sodium influx This specific action on transmembrane calcium movement accounts for its known negative inotropic propensity[4,10] and has been postulated to constitute a distinct antiarrhythmic mechanism[1,4,10,15] Reentrant arrhythmias are now thought to result from slow conduction through discrete segments of partially depolarized fibers[1] and slow conduction appears to be the function of the slow response which is an action potential qualitatively different from the normal sodium mediated spike depolarization [1] The slow response which has electrophysiologic features that are found in the action potentials of the normal sinoatrial (S A) and atrioventricular (A V) nodes appears to be dependent on calcium currents[0,21] The effects of verapamil on calcium dependent electrophysiologic parameters are therefore of particular significance when one considers the drug s mode of action in arrhythmias

Verapamil has a selectively depressant effect on spontaneous rhythmicity of the S A node[4,10,15] and on conduction in the A V node[15] It also suppresses spontaneously active foci in cardiac fibers generating Ca dependent

action potentials resulting in ectopic arrhythmias The observations of Cranefield and colleagues[15] suggest that the drug may exert an equally important antiarrhythmic action by suppressing re entry by its ability to depress conduction of the slow response

The fact that verapamil does not retard the rate of depolarization or repolarization of the action potential[1, 4] is consistent with our own observations that the drug had no effect on the QRS or Q T intervals of the ECG in patients with sinus rhythm The significant prolongation of the P R interval found in our studies as well as in those of others[11, 23] is also in line with the known depressant action of the drug on A V conduction The finding is further supported by electrocardiography of the His bundle[2, 5] which showed that verapamil delayed A V conduction proximal to the His bundle without having an effect on intra atrial or intraventricular conduction The site of maximal delay was in the A V node itself and was found to be largely independent of autonomic influences[25, 2]

The effect of verapamil on A V nodal conduction undoubtedly accounts for its mechanism of action in reducing the ventricular rate in ıtrial flutter and fibrillation as well as for the enhanced A V block or transient periods of A V dissociation found after intravenous injections In our series conversion of atrial flutter and fibrillation to sinus rhythm was achieved rarely and only slightly better reversion rates have been reported by others[2, 3, 27] the fact that the slowing of the ventricular rate when sinus rhythm was not restored by verapamil was relatively short lived would point to a limited usefulness of the drug in the therapy of these arrhythmias However it has been suggested that regularization of the ventricular rate ın ıtrial fibrillation by verapamil might be of hemodynamic benefit especially in cardiac decompensation This phenomenon which was seen in 3 of our patients with atrial fibrillation and which has been explained by Schamroth[12] as resulting from a regulatory or stabilizing effect of verapamil on the A V nodal refractory period is of doubtful therapeutic value Hemodynamic studies have revealed that verapamil produces more marked cardiovascular depression in patients with atrial fibrillation than in patients with sinus rhythm and it is noteworthy that most of our patients in atrial fibrillation sustained significant falls in blood pressure despite a satisfactory slowing of their ventricular rates It is now agreed that atrial flutter is often best treated with direct current countershock[3] but we have found that intravenous verapamil is of diagnostic value in differentiating rapid atrial flutter from SVT when these two arrhythmias are not easily distinguished electrocardiographically If the rhythm is atrial flutter the A V block increases immediately after intravenous verapamil thus revealing the true nature of the arrhythmia

A feature of some interest in the present studies was the observation that 4 of the 11 patients in atrial flutter developed atrial fibrillation after administration of verapamil The mechanism of this action is obscure Verapamil may increase conduction velocity in isolated rabbit atria[10] but this effect was not observed with clinically meaningful concentrations of the drug Furthermore we were unable to show an increase in the flutter rate in our patients including those in whom conversion from atrial flutter to atrial fibrillation subsequently occurred

Intravenous verapamil was found to be disappointing in the treatment of paroxysmal ventricular tachycardia in our series of 5 patients in only one of whom was sinus rhythm restored Significant hypotension after verapamil developed in all 5 patients and for these reasons its use in the management of ventricular tachycardia is not recommended

From the standpoint of advances in therapy perhaps the most important feature of the antiarrhythmic action of verapamil is the prompt and predictable reversion of large numbers of cases of paroxysmal SVT to sinus rhythm In our series 76 per cent of the patients with this arrhythmia had a restoration of sinus rhythm by intravenous verapamil other authors[3, 11, 27, 3] have reported conversion rates between 80 and 100 per cent Many cases of paroxysmal SVT are now known to be due to A V nodal re-entry[32, 33] and therefore the finding that verapamil prolongs the anterograde and retrograde conduction within the A V[4] explains why the drug is very effective in paroxysmal SVT Spurrell Krikler and Sowton[2] have shown prolongation of both anterograde and retrograde conduction within the node during the termination of SVT by verapamil in 6 patients in whom a re entry mech

anism was considered to be responsible for the arrhythmia Furthermore, these authors[27] have shown that verapamil had little or no effect on the anterograde or retrograde conduction through the anomalous pathway in the Wolff Parkinson White syndrome This observation is consistent with our results with verapamil in WPW syndrome with atrial fibrillation, a situation in which fibrillatory impulses may be conducted either through the normal or anomalous pathway but predominantly through the latter [1] In all 3 of our patients, the drug had no effect on the arrhythmia itself or on the ventricular response However Krikler and Spurrell[27] have reported reversion to sinus rhythm in one case of atrial fibrillation complicating WPW syndrome In their case, the conversion to sinus rhythm was preceded by a slowing of the ventricular response and the development of junctional rhythm They speculated that the initial decrease in ventricular rate was due to a blocking action at atrio bypass with a subsequent antifibrillatory effect on the atrium and the restoration of sinus mechanism via a phase of junctional rhythm

The over all experience with verapamil presented here and that reported previously[11, 13, 14, 27] clearly indicate that it is an extremely effective antiarrhythmic agent in paroxysmal SVT, and that its use in this arrhythmia is likely to supersede that of beta adrenergic blocking agents and digoxin in the management of acute episodes In therapeutic doses verapamil does not reduce cardiac output in patients with cardiac disease[2] and when given by slow intravenous injection, would appear to be safer than beta adrenergic blocking agents in patients with reduced myocardial function Furthermore our unpublished experience indicates that direct current countershock after the use of verapamil does not lead to serious postconversion ventricular arrhythmias Hence in situations in which direct current countershock is likely to be indicated should medical treatment be unsuccessful verapamil may be preferred to digitalis Its usefulness is further enhanced by the relatively unimportant side effects noted in our study and in those of others involving large numbers of patients The only side effect noted in our study was a transient and mild fall in blood pressure This has also been the experience of Schamroth[12, 13] and Donnelly and Scamps[14] although the latter authors noted increased dyspnea in 2 patients with obstructive airway disease, even though verapamil has not been found to alter ventilatory functions in asthmatics[18] Moreover, no adverse effects were noted in patients with acute myocardial infarction in our series or in that of Donnelly and Scamps[14] However, there are reports of side effects including hypotension bradycardia and, on rare occasions, ventricular asystole[27, 28, 29] In the majority of these cases, the patients had been on beta adrenergic blocking drugs before verapamil was given, and since the negative inotropic actions and depressant effects on impulse generation of beta antagonists and verapamil are likely to be additive hypotension, bradycardia and asystole are predictable side effects when these drugs are administered in combination Side effects that occur in this context may be reversed by intravenous atropine (may be partially effective), isoprenaline infusion or intravenous calcium (10 to 20 ml of 10 per cent solution) and if necessary, temporary ventricular pacing may be instituted [1]

It is unlikely that prior digitalization is a contraindication to the use of intravenous verapamil since 61 per cent of our patients with arrhythmias and 79 per cent of the patients in Schamroth s series[12] were on cardiac glycosides at the time of the trial It is also emphasized that since verapamil has a depressant effect on impulse generation and on the A V node, it should be used with caution if at all in patients with pre existing disease of the conduction system and in those with sinoatrial disease such as sick sinus syndrome presenting with supraventricular tachycardias[23] On the whole however if adequate precautions are taken in the selection of cases particularly in relation to the concomitant use of beta adrenergic blocking drugs, the use of verapamil is an important and safe addition to existing antiarrhythmic drug regimens The drug is likely to become the initial agent of choice for the acute treatment of most cases of paroxysmal supraventricular tachycardias

Summary

The effects of intravenous verapamil on the electrocardiogram in 15 patients with heart disease in sinus rhythm and in 44 patients with supraventricular and ventricular tachyarrhythmias were evaluated Verapamil prolonged the

P R interval without effect on the QRS duration or the Q T interval In patients with atrial flutter and fibrillation A V block was increased with slowing of the ventricular rate in almost all cases but sinus rhythm was restored in only 1 of 12 patients in atrial fibrillation and in 2 of the 11 patients with flutter Verapamil had no effect in 3 patients with atrial fibrillation complicating WPW syndrome in 1 of 5 patients with ventricular tachycardia it caused reversion to sinus rhythm Sinus rhythm was restored promptly by verapamil in 13 of 17 patients with paroxysmal supraventricular tachycardias in 2 others sinus rhythm became established 1 to 2 hours after administration of the drug Transient hypotension not requiring treatment was the only side effect noted but not in the patients with supraventricular tachycardias in whom blood pressure generally increased after reversion to sinus rhythm by verapamil

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Summary

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Case reports

Systolic prolapse of the mitral valve in Noonan's syndrome

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Portland Ore

Turner s syndrome has been frequently associated with cardiovascular malformations most commonly coarctation of the aorta Noonan s syndrome shares many features with the Turner syndrome but differs in that chromosome studies reveal a normal genotype The cardiac lesion most frequently encountered has been pulmonic stenosis The purpose of this communication is to report a patient who presented with the signs of Noonan s syndrome and was found to have systolic prolapse of the mitral valve with mitral regurgitation

Case report

A thirty five year old Negro woman was admitted for evaluation of cardiovascular disease She had been born prematurely with a birth weight estimated to be four pounds Multiple skin and pulmonary infections were noted in childhood At the conclusion of her only pregnancy at age 5 she gave premature birth to a four pound male infant Cesarean section was performed for obstetric indications and revealed grossly normal internal genitalia

The patient denied all cardiac symptoms There was no history of rheumatic fever There was no family history of congenital malformation or mental retardation

Physical examination revealed a poorly developed Negro woman appearing older than her stated age (height 59 inches weight 8o pounds) Slight frontal bossing ocular hypertelorism (intercanthal diameter 4 5 cm) bilateral ptosis pterygium colli, micrognathia and posteriorly rotated pinnae were apparent on inspection (Fig 1) Also noted were a broad nose with wide ala nasi, a low set posterior hairline and a somewhat low pitched voice The skin was soft and rather hyperelastic The lungs were clear and the liver and spleen were not palpable Pelvic examination revealed no abnormalities Neurologic examination was entirely negative except for mild mental retardation

Examination of the cardiovascular system revealed the pulse to be 84 per minute and regular The blood pressure was 110/60 mm Hg in both arms and 1.0/80 in the lower extremities Jugular venous pulse was normal A slightly hyperactive apex beat was palpable in the fifth left intercostal space at the anterior axillary line On auscultation the first and second heart sounds were normal A loud snapping midsystolic click was heard at the apex and radiated widely A grade III/VI late systolic murmur was heard at the apex It radiated well to the axilla and to the base The click could be moved earlier in systole by standing the patient upright or by inhalation of amyl nitrite

Roentgenographic skeletal survey revealed Perth s disease of the left hip Biomicroscopy and skin biopsy were normal. A buccal smear showed 2(per cent sex chromatin positive Chromosome analysis of 50 blood lymphocytes showed a 46XX pattern

Special studies A phonocardiogram confirmed the auscultatory findings described above Four roentgenographic views of the heart with barium swallow revealed moderate cardiomegaly with enlargement of the left ventricle Left atrial enlargement could not be detected An electrocardiogram (Fig ?) revealed right axis deviation (mean QRS axis in the

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Case reports

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Fig 1 Photograph of patient demonstrating pto is hyper telorism and broad ala nasae

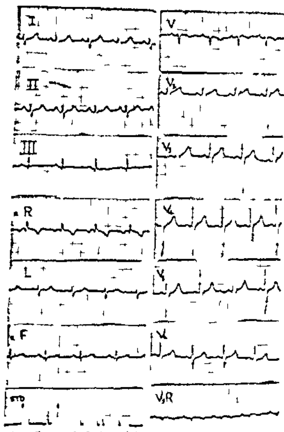


Fig 2 Electrocardiogram showing right axis deviation

frontal plane of plus 120) and clock wise rotation in the horizontal plane Cardiac catheterization revealed a normal resting cardiac index with normal intracardiac and intravas cular pressures Selective cine (60 left anterior oblique projec tion) and cut film biplane retrograde left ventriculography de monstrated systolic prolapse of the mitral valve (Fig 3) with mild to moderate mitral regu gitation In the anteroposterior projection (Fig 4) a localized bulge in the superolateral aspect of the left ventricular wall was seen to project into the cavity of the left ventricle both in systole and in diastole Retrograde ascending aortography revealed a competent aortic valve and a normal thoracic aorta On a subsequent occasion a selective cineangiogram of the right ventricle in the anteroposterior projection showed the outflow tract and pulmonary valve were normal

Comments

In 1963 Noonan and Ehmke[1] reported the com bination of Turner phenotype normal genotype and congenital heart disease in nine children In 1965, Summitt and Opitz[8] proposed that the term Noonan s syndrome be used to designate such patients and that as a group they were separate and distinct from subjects with the Turner syndrome

The more common features of Noonan s syn drome include short stature, hypertelorism ptosis micrognathia, pterygium colli, chest de formities congential heart disease and mental retardation Pulmonic stenosis has been the car diovascular anomaly found in the majority of cases including those originally reported by Noonan [1 5 8 10] However atrial septal defect[2] patent ductus arteriosus,[8] and Ebstein s anoma ly,[10] as well as coarctation of the aorta and aortic stenosis[11] have also been reported with Noonan s syndrome

Until 1961, midsystolic clicks and late systolic murmurs were felt to be extracardiac in origin[12] In the past decade intracardiac phonocardiog raphy has shown convincingly that these auscul tatory phenomena arise from the mitral valve ap paratus[13 15] Angiocardiography has in every reported case revealed systolic prolapse of one or both mitral valve leaflets into the left atrium usually with mild to moderate mitral regurgita tion[6 7 12 13 16 17]

In most instances patients with mitral valve prolapse have no symptoms of cardiac disability and are without other physical abnormalities[18 19] This condition has however been encountered in patients with Marfan s syndrome[13] The patho



Fig 3 Lateral view of systolic frame from selective retrograde left ventriculogram revealing systolic prolapse of a portion of the mitral valve Dye is seen entering the superior portion of the left atrium

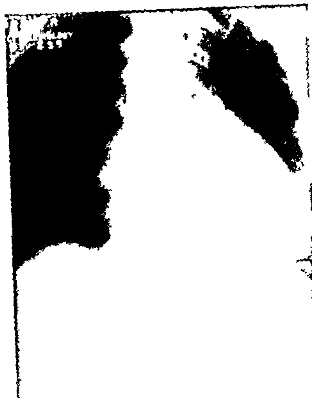


Fig 4 Anteroposterior view showing opacification of left atrium dilation of the mitral valve annulus and a localized bulge in the superolateral aspect of the left ventricular wall

logic findings of mitral valve disease in Marfan's syndrome as well as in the few patients with isolated mitral valve prolapse that have been described include enlargement of the mitral annulus oversized leaflets and thinning and elongation of the chordae tendineae Myxomatous degeneration of the valve substance has been seen on microscopic examination

The angiographic appearance of the bulge in the left ventricular wall of our patient is similar to that described by Ehlers and co workers in 10 patients with the Turner phenotype who had normal chromosome analyses and represents eccentric hypertrophy of the left ventricle The angiograms in their patients also revealed a bulge in the postero inferior surface of the left ventricle which was not seen in our patient With one exception their patients with this left ventricular anomaly had marked superior shift of the QRS axis in the frontal plane (−60 to ± 180) This finding was also not present in our patient None of their subjects were said to have any features of the midsystolic click late systolic murmur syndrome

We have been able to find four cases[3 23] in the literature where either clinical or pathologic evidence of mitral valve prolapse was described in association with the classic Turner syndrome (proved XO genotype and/or gonadal agenesis) The present patient appears to be the first reported instance where mitral valve prolapse has been found in association with Noonan's syndrome

Summary

A thirty five year old woman with Noonan's syndrome (Turner phenotype with normal chromosome pattern) had mitral valve prolapse and mitral insufficiency associated with the auscultatory findings of a midsystolic click and late systolic murmur Selective left ventricular angiocardiography also showed eccentric hypertrophy of the left ventricle To our knowledge this is the

first reported instance of mitral valve prolapse occurring in association with Noonan's syndrome

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Idiopathic calcified apical aneurysm of the left ventricle in an asymptomatic child

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Richard L Shepherd M D
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Reports of isolated idiopathic noncontractile aneurysm of the apex of the left ventricle are uncommon and are scattered geographically[1] reports of idiopathic fibrous aneurysms of the submitral and subaortic portions of the left ventricle originate commonly from Equatorial and South Africa [1] A developmental defect common to apical and subannular aneurysms has been postulated [2]

Case report

A previously well 17 month old black girl born in south Georgia was hospitalized for 10 days with a diagnosis of pneumonia Following successful treatment she was referred to the Cardiac Clinic because *cardiomegaly* was noted on her chest roentgenogram This healthy appearing child weighed 28 pounds and was 30 inches tall The 24 year old mother had no illness in the first trimester of pregnancy Birthweight was 9 [illegible] pounds The general physical examination was normal Arterial and venous pulses were within normal limits The point of maximal impulse of the apex (PMI) presented as a [illegible] amplitude tap in the fifth and sixth left intercostal space just beyond the midclavicular line No ectopic precordial pulsations were noted S_2 was narrowly split No third heart sound was heard No murmurs or atrial gallop sound were present The apexcardiogram showed a small E wave with a poorly defined O point The A wave was small The electrocardiogram suggested extensive para apical involvement showing a Q wave in Leads III aV_F V_5 and V_6 T waves were inverted in the anterolateral precordial leads and the R wave was of decreased amplitude in Leads V_5 and V_6 (Fig 1) The chest roentgenogram showed a slightly enlarged cardiac silhouette suggesting left ventricular enlargement There was no evidence of pulmonary interstitial edema (Fig [illegible]) The hemoglobin was 8 8 grams per cent The sickle cell preparation was negative The iron-deficiency anemia was treated with oral iron

At 18 months of age right and left heart catheterization and selective cineangiography was performed Image intensification fluoroscopy showed a thin curvilinear halo of calcium at the cardiac apex In retrospect the apical calcification could be found on the chest roentgenogram The following pressures in millimeters of mercury were obtained right atrium mean = [illegible] right ventricle 26/5 pulmonary artery 25/9 mean = 15 pulmonary artery wedge pressure a = 11 v = 15 mean = 8 left ventricle 76/7 and aorta 76/4 mean = 54 The arteriovenous oxygen difference was 4 3 c.c s per 100 c c s of blood The cardiac index was 4 1 L per minute per square meter using an assumed oxygen consumption The hemoglobin was 9 4 grams per cent Selective left ventricular cineangiograms in the frontal projection showed an elongated apical aneurysm giving the left ventricular cavity an asymmetrical dumbbell shape (Fig 3 A) A semicircular halo of calcium was noted at the perimeter of the aneurysm wall The apical aneurysm contracted little if any with its greatest diameter changing from 13 to 12 mm in diastole and systole in the neck region of the aneurysm from 8 to 6 mm The diameter of the left ventricle proper changed from 25 to 20 mm in its minor axis (Fig 3 A and B) An aortic root cineangiogram in the frontal view showed the right coronary artery the left anterior descending and the left circumflex coronary arteries to be normal

At 2 years of age she weighed 36 pounds and was 35 inches tall (above the 97 percentile for weight and the 75 percentile for height) The hemoglobin was 12 2 grams per cent Chest x ray showed mild cardiomegaly pulmonary vascular shadows were normal. When 4 years of age she continued well, weighing 44 pounds. No murmur had developed The PMI remained unchanged as a diffuse low amplitude impulse in the fifth and sixth left intercostal space just beyond the clavicular line The parents declined surgical intervention at this time

Discussion

Left ventricular apical aneurysms observed in children tend to fall into two groups The first presents as a complex of congenital defects [3] An epigastric or supraumbilical pulsation is noted as an actively contracting left ventricular apical diverticulum with a well-developed muscular wall presents via an anterior midline defect in the pericardium sternum diaphragm and abdominal wall Nearly all cases have a ventricular septal defect One half have an atrial septal defect and

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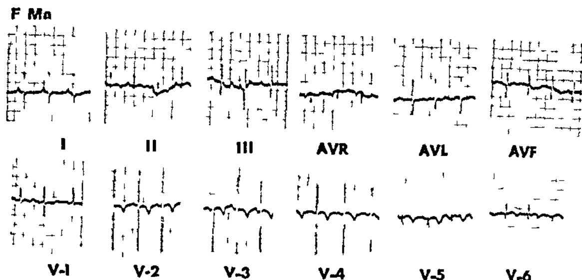


Fig 1 Electrocardiogram suggests inferior and lateral apical dead zone



Fig 2 Chest roentgenogram shows left ventricular enlargement

one third some form of pulmonary stenosis Thus cyanotic heart disease including tetralogy of Fallot may be present Herniation of the anterior leaflet of the mitral valve occurred in a 37 year old physician with infradiaphragmatic apical and posterior wall diverticula of the left ventricle[8]

In the second group, illustrated by our patient, the wall of the apical aneurysm is predominantly fibroelastic tissue of irregular thickness with variable numbers of isolated muscle strands approximately one half of reported apical aneurysms are rimmed with calcium [1,4] No defects of the pericardium, diaphragm or anterior abdominal wall are present and there are no associated congenital or acquired cardiac or coronary artery anomalies Though our patient had no murmurs an apical systolic murmur may be heard Heart failure seems less common in the apical than in subvalvular and lateral wall aneurysms The basal and proximal septal and lateral wall of the left ventricular musculature remains intact dissipation of left ventricular work is minimized by the relatively narrow neck of the aneurysm and mitral valve function is less often seriously disturbed The electrocardiogram is nearly always abnormal showing Q waves loss of R amplitude ST elevation and abnormal T waves Cerebral embolus has been reported in a 13 year old African girl[3] The ages at which the diagnosis of apical aneurysm was made in children were 6 months old (1 case),[7] 18 months (our case) 7 years (3 cases)[1,4,5] 8 years (1 case), and 12 or 13 years (3 cases) [3,6] A fibrous apical left ventricular aneurysm may presumably pass undetected into adult life a 26 year old woman presented with recurrent ventricular tachycardia[9] a 44 year old woman was quite atypical in that a large apical aneurysm was associated with aortic stenosis with a 115 mm Hg peak systolic gradient[10]

The etiology of the apical fibrous aneurysm is not clear This aneurysm may be related to a family of fibrous left ventricular aneurysms described in Africa[1,14] and occurring in order of highest frequency (1) adjacent to the mitral valve

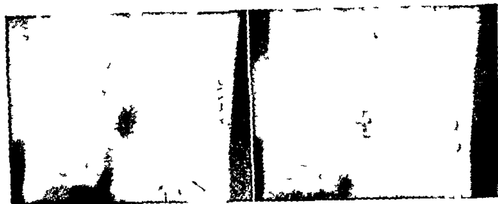


Fig 3 Prints of 16 mm selective left ventricular cineangiogram in the frontal view A Diastolic frame B Systolic frame The size of the apical aneurysm changed little while the neck of the aneurysm narrows slightly No mitral regurgitation is noted Arrows point to the apical halo of calcium

annulus[2] (2) in the subaortic valve annulus area[3] and (3) in the apical region[3] Progressive sac like annular tunneling and loculation results in progressive mitral or aortic valve regurgitation The aneurysms occur where the ventricular walls are thinnest at the apical whorl and at the junction of the left ventricular myocardium with the valve annulus The assumption has been made that a developmental cleft occurs permitting herniation of an endocardial pouch with progressive burrowing about the valve annulus or progressive extrusion at the apex[2,4] Idiopathic annular subvalvular left ventricular aneurysm has been noted in North America in a 13 year old[1] and in a 6-month old Negro infant[1] A congenital submitral left ventricular aneurysm has been described to rupture spontaneously in a 38 hour old white infant Acquired subannular mitral valve aneurysm resembling the African type has been reported in a child following closed chest trauma and has occurred post prosthetic mitral valve replacement[2] Congenital left ventricular aneurysm of the lateral free wall of the left ventricle has been described in this country multiple fatal systemic emboli occurred at 7 and 19 months of age respectively[22,2]

The indications for surgical amputation of the apical fibrous aneurysm include the prevention of systemic embolization recurrent ventricular dysrhythmia or fear of rupture of the potentially thin sac wall as illustrated by the 14 month old child operated upon by Davila and co workers

Summary

To our knowledge this is the eighth reported case of isolated idiopathic noncontractile apical left ventricular aneurysm in the child Referral to the physician is likely to be made because of a systolic murmur unusual cardiac contour, cardiomegaly or apical calcification on chest x ray or rarely a systemic embolus Heart failure is uncommon The electrocardiogram shows abnormal Q waves and/or inferior and lateral ST T changes Careful image intensification fluoroscopy will demonstrate apical calcification in one half of the cases

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Clinical pathologic conference

Sudden appearance of a systolic murmur in acute myocardial infarction

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Case presentation

The patient was a 57 year old male painting contractor who had been well until the day of admission to the hospital While attending the funeral of his mother who had died suddenly of a myocardial infarction the patient developed severe pressing retrosternal chest pain The pain persisted throughout the day and was associated with diffuse sweating and aching in both elbows He experienced no nausea palpitations or feelings of lightheadedness About 10 hours after the onset of the pain the patient came to the hospital emergency room where his electrocardiogram (ECG) was abnormal and he was admitted

Apart from a history of kidney stones diagnosed approximately 10 years previously review of organ systems was generally unremarkable The patient did not have a history of hypertension diabetes heart murmur or hypercholesterolemia He smoked three packs of cigarettes per day For the past 6 or 7 months the patient had noted some mild swelling of his ankles and had taken small amounts of some diuretics that his wife had In addition to his mothers heart disease other members of his family had had coronary artery disease although the patients father was 80 years old alive and well

The patient was a markedly obese male he was 6 feet tall and weighed 240 pounds The blood pressure was 110/80 mm Hg in both arms the heart rate was 80 and the respirations were regular at 18 per minute He was bald His head eyes ears nose and throat were unremarkable with good strong equal carotid pulses without bruits There was no thyromegaly present Chest examination showed that diaphragms appeared to move poorly and were somewhat depressed There were bilateral crackling rhonchi and basilar rales which did not clear with coughing occasional respiratory wheezes were also heard

Cardiovascular examination demonstrated normal jugular venous pulsations and the veins were not distended There were no precordial heaves or thrills The apex beat was poorly felt and appeared to lie in the midclavicular line in the fifth intercostal space The first and second heart sounds were soft with an intermittent fourth heart sound being present The third heart sound was not present There were no murmurs clicks or friction rubs Abdominal examination revealed no distinct organomegaly and the results of neurologic examination were also unremarkable All peripheral pulses appeared normal

The ECG revealed a normal sinus rhythm with ST segment depression in Leads I aV_L V V_3 V_4 V and V There was an increased amplitude to the T wave in Leads II III and aV_F An ECG later on the day of admission revealed a deep Q wave in Lead III a small Q wave in Lead aV_F with T wave inversions in Leads III and aV_F and flattening of the previously elevated T wave in Lead II By the following day the patient had clear cut evidence of an inferior myocardial infarction on ECG The chest roentgenogram on admission showed the heart size to be marginally increased without pulmonary vascular congestion The serum creatine phosphokinase (CPK)

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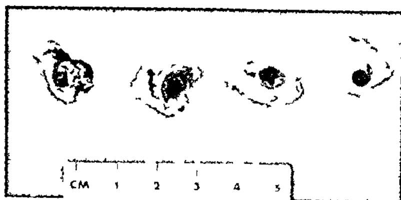


Fig 1 Four transverse segments of the proximal right coronary artery showing occlusion by a recent thrombus



Fig 2 Opened left ventricle showing the anterior leaflet of the mitral valve (M) intact anterior papillary muscle (A) and ruptured posterior papillary muscle (P) The arrowheads point to the two separate torn muscle bellies.

holosystolic murmur which was heard best at the apex and radiated slightly into the axilla after acute myocardial infarction Because there was no evidence of heart failure these patients were carefully observed and managed conservatively The murmurs have gradually decreased in intensity so that later many of these patients have only a midsystolic click without a murmur except in the presence of an anginal attack It is important also to remember that patients who have angina pectoris may develop a murmur of mitral insufficiency during their episode of pain When this murmur is heard during the course of AMI one must be sure that it is not just a transient phenomenon but one that is of great hemodynamic importance and requires urgent action The fact that this patient had a murmur heard at the time he was transferred back to the coronary care unit when he was in pulmonary edema would suggest from a clinical standpoint that he had a *ruptured papillary muscle complicating an inferior myocardial infarction*

Pathologic findings

DR. LIE Postmortem examination showed an enlarged heart weighing 500 grams with an extensive recent inferior wall infarction which extended from the apex to the base The left anterior descending and the left circumflex coronary arteries showed focal 75 per cent +

on admission was 104 I U per liter (normal, 35 to 175 I U per liter) the glutamic oxalacetic transaminase was 18 I U per liter (normal 5 to 30) and lactic dehydrogenase was 124 I U per liter (normal 75 to 175) Twelve hours later the CPK rose to 408 and 24 hours after admission was 1 208 I U per liter By the second hospital day, the CPK had fallen to 420 I U per liter

The initial course of this patient was unremarkable During his stay in the coronary care unit no arrhythmias were noted and the blood pressure was stable He had no recurrence of chest pain Seventy two hours after admission to the hospital the patient was transferred to the general ward in seemingly stable condition At 2 A M on the fourth hospital day, the patient began to complain of a further episode of chest pain He was given sublingual nitroglycerin which did not relieve the pain At that time he was examined and found to be sweaty with a blood pressure of 110/90 mm Hg and a pulse of 88 per minute There were bilateral rales heard to the midscapular areas with a slight prolongation of the expiratory phase The respirations were labored The heart sounds were distinct and no murmurs were detected The patient was transferred back to the coronary care unit, where it was noted that his blood pressure had fallen 100 mm Hg systolic and was barely palpable For the first time, a distinct Grade 3/6 late systolic murmur was heard at the left sternal border and at the apex Over a matter of several minutes this murmur increased in intensity became louder, and the patient suffered ventricular fibrillation All attempts at resuscitation failed

Clinical discussion

Dr Wright This patient presented with a history and laboratory findings which were compatible with the diagnosis of acute myocardial infarction (AMI) It is interesting that this patient had no prior history of chest pain on exertion Although he was obese and a heavy cigarette smoker, no other risk factors were present He apparently had suffered the myocardial infarction about 10 hours before coming to the hospital and at the time of admission had ECG changes which indicated the early stages of evolution of his AMI Among patients with AMI who survive the initial episode and make it to the hospital we anticipate a mortality rate of approximately 15 to 20 per cent Since the advent of continuous monitoring in coronary care units most of these deaths are related to pump failure and cardiogenic shock During this patient s first 3 days in the hospital there was no evidence of major complication Since he had an inferior myocardial infarction, it was felt that he was stable enough to be moved out of the intensive care unit for convalescence

Potentially fatal complications of AMI must be considered when discussing this case Shortly after admission to the hospital, although often in the presence of arrhythmias patients in a seemingly stable condition may have a gradual fall of blood pressure decrease in urinary output, and eventually manifest the clinical pattern of cardiogenic shock This may or may not be associated with specific structural abnormalities of the heart, other than the size of the myocardial infarction Other untoward events that can happen early in the course of AMI, especially in the presence of an anteroseptal myocardial infarction and a sudden fall in blood pressure or the abrupt onset of heart failure include rupture of the ventricular septum and rupture of the free wall of the left ventricle In the instance where the patient is suddenly in shock and maintains normal sinus rhythm perforation of the free wall of the left ventricle with cardiac tamponade should be considered Both of these latter two complications are difficult to manage, and when they do occur, except under the most ideal situations they are usually fatal

Another structural complication that may occur early in the course of AMI is rupture of a papillary muscle due to ischemic necrosis This complication may be detectable at the bedside and if recognized early in its course frequently mitral valve replacement can be done with some success The clinical setting of ruptured papillary muscle in AMI is that of inferior or lateral wall myocardial infarction, an initially stable condition and then sudden onset of heart failure with the appearance of a new systolic murmur This complication often is accompanied by new or recurrent chest pain The diagnosis is made easier if the patient has been observed and found not to have a heart murmur

Similar murmurs may develop in people with AMI who do not develop heart failure in such instances the patients can be treated conservatively We have followed several patients of this type In each instance the patient developed a



Fig 1 Four transverse segments of the proximal right coronary artery showing occlusion by a recent thrombus



Fig 2 Opened left ventricle showing the anterior leaflet of the mitral valve (*M*) intact anterior papillary muscle (*A*) and ruptured posterior papillary muscle (*P*) The arrowheads point to the two separate torn muscle bellies.

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Fig 3 Photomicrograph showing acutely infarcted posterior papillary muscle the torn surface is covered by a thick layer of fibrin coagulum (*F*) (Hematoxylin and eosin stain)



Fig 4 Photomicrograph of a wall of a segment of the right coronary artery showing a thick fibrotic intima (*I*) with disrupted atheromatous plaque (*A*) and focal necrosis of the media (*M*) as indicated by arrows Note that the thrombus (*T*) in the left upper corner contains acicular cholesterol clefts (Hematoxylin and eosin stain)

atherosclerotic luminal narrowing in their proximal 1 to 1 5 cm segments The right coronary artery was completely occluded by a soft dark red thrombus at 6 cm from its ostium immediately proximal to a segment of the artery which showed 90 per cent + atherosclerotic luminal narrowing (Fig 1) As Dr Wright has predicted, the opened heart revealed that the inferior wall infarction included the posterior papillary muscle which had ruptured at the midpoint between the tip and the base (Fig 2) There were no pulmonary thromboemboli but the lungs showed severe pulmonary edema and congestion with a combined weight of 2 040 grams Marked passive congestion was also present in the liver spleen and kidneys

On microscopic examination the myocardial infarction was in the age range of 4 to 5 days histologically, thus in complete accord with the chronology of the patient s clinical presentation The avulsed posterior papillary muscle showed a

homogeneous transmural infarction with interstitial hemorrhage and a marked polymorphonuclear infiltrate The torn surface of the papillary muscle was covered by a thick layer of fibrin coagulum (Fig 3) The thrombus in the right coronary artery was barely adherent to the endothelial lining of the vessel wall with little evidence of organization The thrombus contained acicular cholesterol clefts and appeared to be related to ruptured intimal plaque Of interest was the finding of an acute inflammatory reaction and focal necrosis of medial smooth muscle cells in the severely atherosclerotic segment of the right coronary artery distal to the occlusive thrombus (Fig 4) The combination of the clinically documented hypotensive episodes and the presumed compromised perfusion of vasa vasorum following coronary thrombosis upstream to these vascular abnormalities were probably responsible for the observed changes

Major anatomic diagnosis

1 Acute inferior myocardial infarction with ruptured posterior papillary muscle cardiomegaly (500 Gm)
2 Acute pulmonary edema
3 Severe atherosclerosis of coronary arteries with recent thrombosis of the right coronary artery

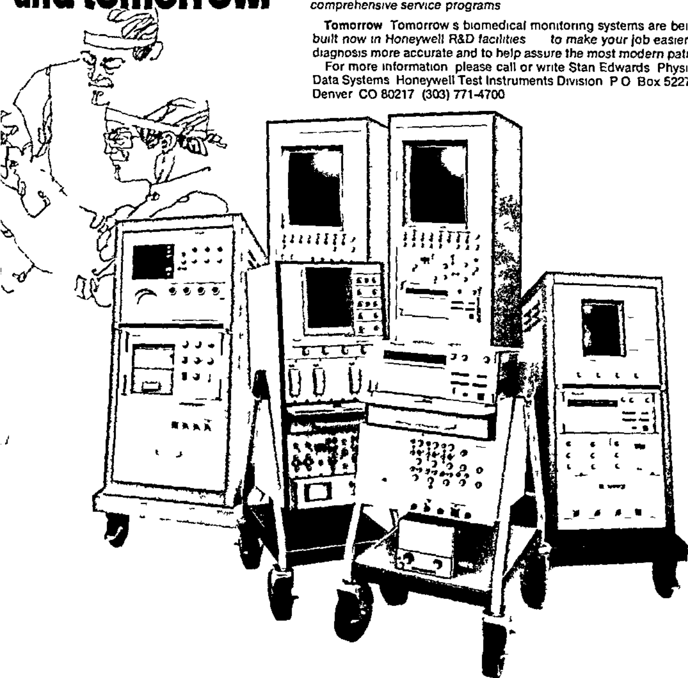
Concluding comment

DR LIE Ruptured papillary muscle complicating AMI is an uncommon and dramatic clinical event and a striking pathologic finding as was exemplified by this case presentation Although infarction and fibrosis of the papillary muscles of the left ventricle occur not infrequently ruptured papillary muscle is a rare complication of AMI and the reported incidence ranged from 0 32 to 0 95 per cent That the posterior papillary muscle ruptures several times more commonly than the anterior papillary muscle can be attributed to a better collateral circulation in the latter Patients with ruptured papillary muscle usually die within 24 hours and 80 per cent die within two weeks[5] The sudden occurrence of mitral regurgitation in an already severely handicapped (acutely infarcted) left ventricle often precipitates fatal pulmonary edema Ruptured papillary muscle may be detectable at the bedside[6] and survival from this dreaded complication of AMI might be possible if it is recognized early Davidson[7] reported the first antemortem diagnosis of ruptured papillary muscle in 1948 and the first successful surgical intervention was described by Austen and associates in 1965 In the past decade the number of life saving mitral valve replacements with or without emergency aortocoronary bypass graft and resection of the akinetic left ventricular wall has grown [2] Although it is the consensus that the optimal time for surgery is in the 2 week to 2 month postinfarction period when patients are in a more stable condition[9, 1, 2] [2] emergency operations performed within 5 to 7 days after myocardial infarction also have been highly successful.[9]

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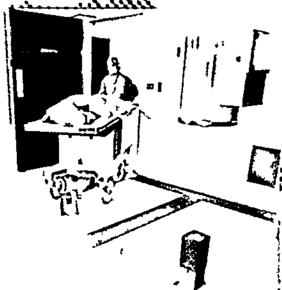
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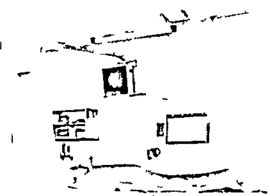
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Fundamentals of clinical cardiology

Orthostatic hypotension Mechanisms and management

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Dizziness light headedness and syncope are complaints of patients with impaired cerebral circulation When these symptoms occur exclusively in the upright posture orthostatic hypotension is commonly present

In man in the upright position the long axis of the body is parallel to the gravitational pull and *approximately 300 to 800 ml of blood* are pooled in the lower limbs The considerable shift of blood out of the thorax initiates a sequence of events which if left unchecked will produce a serious fall in arterial pressure The reduction in central blood volume reduces the filling pressure of the right ventricle In absence of neurogenic and other adjustments the decrease in filling pressure would result in a lesser distension of the heart during diastole and as a consequence there would be a decrease in stroke volume cardiac output and arterial pressure

Man s ability to maintain consciousness in the upright position is dependent mainly on the autonomic nervous system and on baroreceptor reflexes Assuming the upright position is followed by an immediate fall in arterial pressure secondary to diminished cardiac filling (Fig 1) The initial hypotension is sensed by the baroreceptors present in the carotid sinuses and aortic arch. This will result in a diminution in the rate and frequency of the inhibitory impulses arising from these areas to the vasomotor center (VMC)

Due to decrease of baroreceptor drive, an increase in the tone of the adrenergic sympathetic nerves should occur with consequent effects on peripheral blood vessels and heart function—viz arteriolar constriction and cardiac acceleration Further there are evidences that low pressure baroreceptors present in the cardiovascular system may play a role in the vasoconstrictor responses to venous pooling[2]

Beside the autonomic nervous system increased tone and isotonic contractions of skeletal muscles in the lower limbs during standing will force the blood past the venous valves toward the heart Activation of this muscle pump is an important mechanism which enhances venous return and prevents a serious fall in cardiac output[2] Further hyperventilation which commonly occurs while changing posture produces a reflex increase in venous tone that helps cardiac filling

To investigate the role played by the autonomic nervous system in postural adjustments we compared the hemodynamic changes produced by head up tilt in seven patients with idiopathic orthostatic hypotension (IOH) to the changes in 17 normal subjects.[3] While normal subjects were able to keep their arterial pressure similar to the supine level patients had an average fall in systolic pressure of 55 mm Hg (39 per cent) and in diastolic pressure of 22 mm Hg (28 per cent) The reduction of pressure in patients was associated with a decrease in cardiac output by 36 ± 3 7 per cent (mean ± S E) more marked than that seen in normal subjects (13 ± 2 8 per cent) Changes in

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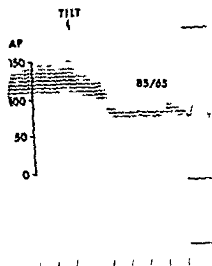


Fig 3 *Effect of head up tilt (60 degrees) on arterial pressure (AP) in a patient with IOH*

TESTS OF AUTONOMIC CARDIOVASCULAR REACTIVITY

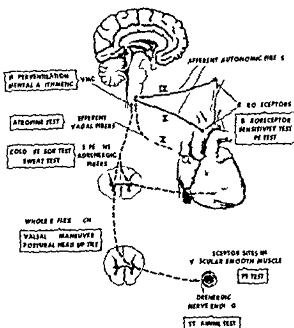


Fig 4 Tests of autonomic function. Components of baroreflex arc and methods of their investigation. *PE* Phenylephrine *For details consult reference number 9*

fere with the efferent pathways The same mechanism might be present in cases of porphyria[8] and patients taking L dopa In amyloidosis the lesion is in the arteriolar wall

To determine the site of the defect in the baroreceptor reflex different physiologic tests are utilized (Fig 4) The details of these tests were discussed in a previous communication

Clinical picture of orthostatic hypotension secondary to autonomic nervous insufficiency

IOH provides a classical example of postural hypotension due to interruption of the integrity of the baroreceptor reflex It is a relatively rare disease however it is important to differentiate it from other causes of episodic disturbances in consciousness IOH is a disease of late middle age the median age in our series was 62 years It runs a progressive fluctuant course with periods of remissions and relapses The main symptoms are secondary to cerebral ischemia induced by the upright posture Patients complain of fainting spells blackouts transient blindness dizziness and/or syncopal episodes which may be associated with convulsions The loss of consciousness is usually dramatic with no prodromes although some patients may complain of aching or sharp pains in the shoulders occipital and/or frontal muscles before they faint Since IOH is a disease of the autonomic nervous system other symptoms related to the involvement of various organs are present Impotence is common in males failure to maintain erection is noted first followed later by failure to start it Lack of sweating over patchy or diffuse areas of the skin is usual one of our patients had a heat stroke 20 years before his symptoms of postural hypotension Bowel and bladder disturbances are frequent Involvement of the extrapyramidal system and the presence of signs of Parkinsonism may be combined with IOH and the syndrome is called Shy Drager In its advanced form the disease is incapacitating and the patient becomes completely bed ridden because of the severe postural symptoms the mere sitting in bed may induce fainting.

The diagnosis is based on the clinical picture and the absence of a cause for postural hypotension There is an abnormal response to the Valsalva maneuver (Fig 5) The site of the defect in the baroreceptor reflex arc is usually in the efferent —rarely the afferent—limb

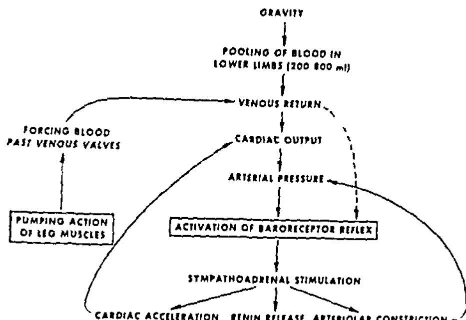


Fig 1 Effects of gravity and physiologic adjustments operating while standing to maintain arterial pressure

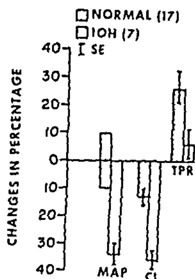


Fig 2 Changes in mean arterial pressure (*MAP*) cardiac index (*CI*) and total peripheral resistance (*TPR*) produced by head up tilt in normal subjects and patients with IOH

peripheral resistance varied widely among patients it increased by an average of 7 per cent, in marked contrast with the rise of 26 per cent in normal subjects (Fig 2) Fig 3 shows the effect of head up tilt on arterial pressure in a patient with IOH *It is obvious that patients with autonomic nervous insufficiency fail to raise their systemic peripheral resistance and have an exaggerated fall in cardiac output while standing Both factors contribute to the severe postural hypotension*

Mechanisms and causes of orthostatic hypotension

Orthostatic hypotension is most likely to develop when there is autonomic nervous dysfunction interrupting the baroreceptor reflex arc or when there is a serious reduction in the effective circulating blood volume or rarely as a result of the presence of circulating vasodilator substances—the syndrome of hyperbradykininism

Interruption of the baroreceptor reflex arc This is probably the most common and the most important mechanism of orthostatic hypotension Failure of this reflex may be due to lesions in the afferent limb in the VMC, in the efferent adrenergic limb or in the arteriolar wall itself In tabes dorsalis some cases of IOH,[6] and diabetes mellitus[7] the defect is most probably in the afferent limb

Involvement of the VMC can be secondary to vascular lesions of the brain stem tumors or swellings near the VMC (tumors of the fourth ventricle) demyelinating or degenerative diseases of the central nervous system Drugs like tranquilizers sedatives hypnotics, and antidepressants can produce postural hypotension possibly through direct depression of VMC Further the phenothiazines block the actions of epinephrine and norepinephrine but the exact mechanism of their action on the autonomic nervous system is unknown [8]

Spinal trauma degenerative or demyelinating diseases of the spinal cord and extensive sympathectomies interrupt the efferent adrenergic pathways The majority of cases of IOH[9] are probably secondary to efferent adrenergic dysfunction Antipressor medications especially ganglionic blocking agents and guanethidine inter

Table I Causes of episodic disturbances in con sciousness (other than orthostatic hypotension)

A *Postural*
1 Vaso agal vasodepressor (common faint)
2 Hypersensitive carotid sinus
3 Micturition syncope
4 Left atrial myxoma
5 Excessive orthostatic tachycardia in hyper beta adren ergic state
6 Hysteria

B *Nonpostural*
1 Cardiac arrhythmias
2 Severe stenotic valvular lesions idiopathic hypertrophic subaortic stenosis
3 Cerebrovascular insufficiency subclavian steal syn drome
4 Epilepsy—petit and grand mal
5 Hypoglycemia
6 Recurrent pulmonary embolization
7 Hyperventilation

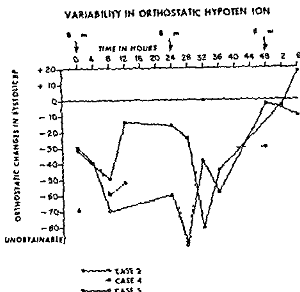


Fig 6 Degree of orthostatic fall in systolic arterial pressure in three patients with IOH during hospital course Variability in postural hypotension is shown with no diurnal pattern

drome occurs in two forms (1) familial and (2) in association with the dumping syndrome following gastric surgery The clinical picture is similar in both types Orthostatic syncopic attacks are char acteristically exacerbated after meals Facial erythema is present with ecchymosis and purple discoloration of the legs while standing Ortho static hypotension is accompanied with severe tachycardia and very small pulse pressure The intervals between the spells are quite variable and it may be difficult to precipitate them

The etiology of hyperbradykininism is pre sumably impaired destruction of circulating bradykinins An enzymatic defect has been demonstrated Medications that have proved helpful in the treatment of this condition are propranolol 9 α fluorohydrocortisone and cypro heptidine

Management of orthostatic hypotension

Patients presenting with symptoms suggestive of orthostatic hypotension should be studied in a systematic way (1) to establish the presence of the condition and to rule out other causes of episodic disturbances in consciousness and (2) to identify mechanisms and to discover the potenti ally curable forms of the disease

A careful history and a good physical examina tion are the first step in the work up of a suspected case of postural hypotension The development of symptoms of cerebral ischemia should be related exclusively to postural fall in arterial pressure It is obvious that complaints of faintness or syncope present while the patient is lying flat on his back are against the diagnosis of orthostatic hypotension unless an additional concomitant disease is present On the other hand there is no magic figure that defines the degree of fall in arterial pressure which consti tutes orthostatic hypotension A decrease of 30 mm Hg or more in systolic and/or 20 mm Hg or more in diastolic pressure are arbitrary figures that are sometimes used However it is the association of symptoms of cerebral ischemia with postural decrease in arterial pressure which really matters

The marked variability in the symptoms and the degree of postural hypotension as shown in Fig 6 necessitate frequent blood pressure mea surements The absence of postural fall in pres sure on one or two occasions does not rule out the presence of the condition Sometimes it is neces sary to have the patient hospitalized and have his arterial pressure checked repeatedly supine and standing In some patients the postural fall in pressure is not immediate and it takes few minutes of standing before hypotension occurs For this reason whenever the possibility of orthostatic hypotension exists it is important to wait for at least 5 minutes Physical exercise is sometimes performed before checking the stand ing pressure in order to make hypotension mani

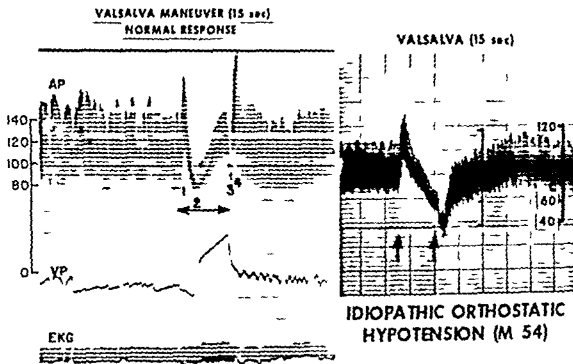


Fig 5 Responses to Valsalva maneuver in a normal subject and in a patient with IOH

Hypovolemia

A decrease in effective circulating blood volume can predispose to orthostatic hypotension Since sympathetic activity is increased when there is a reduction of blood volume postural hypotension becomes more marked if hypovolemia is combined with defective autonomic nervous function Decreased venous filling of the heart will add to the effect of gravitational pooling in the lower limbs while standing and brings a sharp decrease in cardiac output Autonomic compensatory reflexes may be overpowered and fail to maintain arterial pressure Epstein Stampfer and Beiser[11] proposed another mechanism to explain postural syncope induced by interventions which decrease effective blood volume a combination of a diminution in ventricular volume and increase in sympathetic tone results in an increase in ventricular wall tension Such an increase in ventricular wall tension may then trigger a depressor reflex initiated by intracardiac baroreceptors

Hypovolemia responsible for orthostatic hypotension may be absolute e g , following massive diuresis severe fluid loss or gastrointestinal bleeding Relative hypovolemia is present when there is no actual reduction in total blood volume but because of excessive venous pooling in the lower extremities there is a diminution in the effective blood volume The latter condition is present in patients with extensive varicose veins in lower limbs or following certain drugs like nitrites Postural hypotension in adrenocortical insufficiency might be the result of more than one factor reduction in blood volume impaired myocardial contractility, and/or impaired responsiveness of arterioles to norepinephrine Again the mechanism of postural hypotension in some patients with pheochromocytoma is not clear

Orthostatic hypotension secondary to hypovolemia is associated with marked postural tachycardia, whereas the latter is absent or only minimal in patients with autonomic nervous dysfunction Further patients with hypovolemia have a normal response to the Valsalva maneuver

Drugs that depress the sympathetic nervous activity or conditions associated with sluggish or inadequate function of the regulating mechanisms e g prolonged recumbency physical exhaustion starvation and old age can exaggerate the postural effects of hypovolemia

Circulating vasodilators Hyperbradykininism

This is a very rare mechanism of orthostatic hypotension[12] We have had the opportunity to see only one case of this newly described syndrome It is due to the presence of excessive circulating bradykinins These kinins are peptides with very potent vasodilator effect The syn

(tumors or swellings in the fourth ventricle) The diagnosis of hyperbradykininism depends on the clinical characteristics together with the demonstration of high plasma concentration of bradykinin

Symptomatic treatment of orthostatic hypotension

Since a large number of patients with orthostatic hypotension have either an incurable or an unidentified cause the treatment will be only symptomatic

Patients should be encouraged to keep ambulant and to be as active physically as they can Because of its unfavorable and deleterious effect on the course of postural hypotension prolonged recumbency should be avoided Similarly patients should be instructed against standing still and sudden postural changes It is recommended to raise the head of the bed at time of sleep Elastic stockings that fit tightly to the lower extremities have proved helpful in our experience To be effective the stockings should reach up to the groin and be used all day when the patient is standing

Postural exercises—frequent supine and standing postures several minutes each time to be done daily or with the help of a tilt table—may have some benefit We found a decrease in the degree of postural fall in arterial pressure after repeated tilting at the same setting Table II shows the results of repeated tilting on a tilt table in a patient with IOH The patient was head up tilted to the same degree (60 degrees) for 5 minutes then tilted back to the horizontal level (0 degrees) for 10 minutes Arterial pressure was checked while supine immediately after head up tilt and 5 minutes later The table shows the progressive fall in the degree of postural hypotension after repeated tilting

Patients should be advised against the use of sedatives, hypnotics tranquilizers and diuretics On the other hand excessive salt (sodium chloride) intake should be encouraged We recommend 20 to 30 Gm of sodium chloride to be added to food daily (this is about two to three times the usual daily intake) We found that this regimen combined with mineralocorticoids was helpful in three patients with severe orthostatic hypotension however it carries the danger of increasing body weight precipitating supine hypertension edema and possibly cardiac failure

Table II Results of repeated tilting on arterial pressure

No of tilts	*Control (supine 0)*	*Tilt (head up 60)*		*Symptoms (after 5 min)*
		1 min.	*5 min.*	
1	136/86	100/64	64/52	Syncope
2	1[illegible] 90	108/70	68/[illegible]4	Syncope
3	134/90	110/72	80/6[illegible]	Blackout dizziness
4	134/88	108/72	94/76	None
5	136/90	1[illegible]/80	114/80	None

Drug therapy

There is no single drug that proved effective in the treatment of orthostatic hypotension Oral sympathomimetics like ephedrine hyamine ara mine and similar drugs are generally prescribed but in our experience their effectiveness is unpredictable however they should be given a trial Mineralocorticoids have already been referred to 9 α fluorohydrocortisone (Florinef) is the one we use Besides producing salt and water retention and expanding the blood volume—an effect which helps venous filling of the heart—it may increase the responsiveness of arterioles to the neurotransmitter[13]

Recently there are claims that tyramine rich foods combined with monoamine oxidase inhibitors are effective in the treatment of resistant cases of IOH but results were not encouraging when this regimen was tried in two of our patients

All kinds of drug therapy carry the danger of precipitating hypertension Frequent observation of arterial pressure at weekly intervals is recommended When Florinef is prescribed one should start with a small dose (0 1 mg per day) which can be increased gradually according to therapeutic response

In conclusion the treatment of orthostatic hypotension still presents a challenging problem The aim should be to keep the patient active and ambulatory as long as possible

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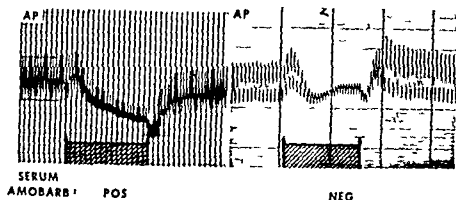


Fig 7 Results of the Valsalva maneuver and coma profile in a patient with orthostatic hypotension In the figure to the left there is an abnormal response to the Valsalva maneuver and serum is positive for amobarbitone On the right amobarbitone was discontinued with recovery of the normal response to the Valsalva maneuver and cure of the orthostatic hypotension

fest Arteriolar dilatation produced in the exercising muscles can precipitate orthostatic hypotension when it is latent

The similarity between the symptoms of postural hypotension and other causes of episodic disturbances in consciousness can be close The differentiation may be difficult, particularly when the disturbance in consciousness is related to posture Absence of prodromes and the constant relationship between fall in pressure and standing are present in orthostatic hypotension Table I shows a number of conditions other than orthostatic hypotension which produce episodic disturbances in consciousness

Identification of mechanisms and etiology

Arterial pressure responses to the Valsalva maneuver and postural changes in heart rate are helpful to separate patients with autonomic nervous dysfunction from those with hypovolemia or bradykininism Impotence, bladder and bowel disturbances or neurologic symptoms are present in the first condition Measurement of the total blood volume may be required in some cases to rule out hypovolemic states when the diagnosis is in doubt, although we found that patients with IOH had a smaller blood volume than normal[3] The possibility of drug intake should be always kept in mind since drugs are frequent and important causes of postural hypotension Medicines like tranquilizers antidepressants and hypnotics may be denied or forgotten by many patients A female patient was referred to us because of recurrent fainting spells during the past 4 years These spells were present in the absence of any obvious cause and were diagnosed secondary to orthostatic hypotension—possibly idiopathic She had an abnormal response to the Valsalva maneuver which suggested interruption of the baroreceptor reflex arc (Fig 7) In spite of her denial of any drug intake analysis of her blood sample for a coma profile was positive for amobarbitone When the patient was put under careful nursing observation—making sure that she had no access to the drug—her symptoms disappeared the Valsalva maneuver showed a normal response and the blood was negative for amobarbitone (Fig 7) We suggest that a coma profile should be done in every patient presenting with postural hypotension

It is important to identify, in addition to drug intake other potentially curable conditions like adrenocortical insufficiency and hypovolemic states Measurement of 17 hydroxy, 17 ketosteroids and plasma cortisol is indicated in patients who have a normal response to the Valsalva maneuver and a small blood volume The rare cases of pheochromocytoma presenting with postural hypotension are difficult to miss, however, estimation of urinary metanephrines and vanillyl mandelic acid are necessary whenever this condition is suspected Tests for syphilis, porphyria diabetes, and amyloidosis besides measurement of serum electrolytes are part of the general laboratory work up Brain scan, skull x ray electroencephalogram, and cerebral angiographic studies may be needed whenever there is a possibility of a brain tumor near the VMC

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Electrophysiology and pharmacology of cardiac arrhythmias IX Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade Part A

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The effects of the sympathetic nervous system on the heart are partly or wholly responsible for many cardiac arrhythmias and pharmacological agents which interfere with these actions may therefore be antiarrhythmic Of all the drugs which can prevent or counteract sympathetic effects on the heart the beta receptor blocking drugs have achieved the greatest usefulness as antiarrhythmic agents In order to comprehend how these drugs exert a cardiac antiarrhythmic effect an understanding of the electrophysiological effects of sympathetic activation and catecholamines is required We first will consider these effects and then discuss the antiarrhythmic properties of beta receptor blocking drugs In addition beta receptor blocking drugs affect cardiac electrophysiology by means other than sympathetic inhibition and the importance of these actions also will be considered

I The sympathetic innervation of the heart

The human heart is richly innervated by the sympathetic nervous system The cardiac branches of the sympathetic trunk arise in the cervical and thoracic regions and contribute to and form the cardiac plexi which lie on the anterior and posterior walls of the pulmonary truncus Extensions of these pulmonary plexi form additional nerve networks over the atria and ventricles The postganglionic sympathetic fibers from these nerve networks innervate all types of cardiac fibers although they are most dense in the sinus and atrioventricular (AV) nodes Adrenergic nerve fiber density also is high throughout the atria although not to the extent seen in the nodes Ventricular muscle fibers receive extensive sympathetic innervation but the density of nerve endings varies markedly in different regions[3] Compared to other regions of the heart the Purkinje system appears to have only limited adrenergic innervation[4]

II The beta adrenergic receptors

The catecholamine norepinephrine is released from post ganglionic sympathetic nerve terminals on activation of these nerves In 1906 Sir Henry Dale postulated that catecholamines interact with receptors on the effector organ to cause their physiological effect[5] Subsequent studies by Ahlquist[6] demonstrated that functionally there appears to be two types of catecholamine receptors on effector organs (1) an adrenergic receptor which, when activated usually gives rise to an excitatory response such as the hypertensive response to norepinephrine resulting from arteriolar constriction and (2) an adrenergic receptor which in most tissues is responsible for an inhibitory response such as the hypotensive response to epinephrine due to arteriolar dilatation The excitatory receptor was termed the alpha receptor and the inhibitory receptor the beta receptor Some tissues have variable numbers of both

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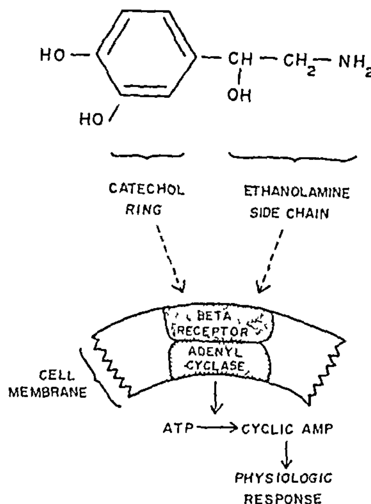


Fig 1 Schematic representation of the mechanism of catecholamine action The structure of the catecholamine norepinephrine is shown above Binding of the catechol at the ring hydroxyls to the beta receptor on the cell membrane is probably an important factor in activating the receptor The ethanolamine side chain of the catecholamine molecule may be an additional binding site Binding of the catecholamine molecule to the beta receptor activates adenyl cyclase located in the membrane which converts ATP to cyclic AMP This results in the physiologic response (Adapted from Lefkowitz R J Isolated hormone receptors physiologic and clinical implications N Engl J Med 288 1061 1973)

receptors others have only one receptor type Although the heart contains mostly beta receptors in this organ beta receptor stimulation results in an excitatory (e g increased contractility, rate etc) rather than an inhibitory response These responses are blocked by beta receptor blocking drugs

The identity of the catecholamine beta receptor and how it functions to cause a physiological response when it interacts with catecholamines have been the subject of intense investigation for many years [7] These investigations have suggested that the beta receptor is probably composed of protein binding sites with crucially located sulfhydryl groups located on the outer surface of the cell membrane Once norepinephrine is released from the nerve terminal, it may bind to the outer surface of the cell membrane at these binding sites (Fig 1) Binding of the neurotransmitter may occur at several distinct points of contact One likely point of attachment is at the catechol ring which might be bound through the two ring hydroxyls [7] Experimental evidence suggests an additional binding site which is specific for and attaches to the ethanolamine side chain of the catecholamine molecule (Fig 1) No structural alterations of the catecholamine molecule occur consequent to its binding to the cell membrane and it is not consumed by virtue of its reaction with the receptor

Beta adrenergic receptors in different tissues may have different properties The beta receptors in the heart have been designated as $beta_1$, those in other tissues as $beta_2$ based in part upon their different susceptibility to blockade by certain beta blocking drugs (see below) Although this concept is still in the investigative stage a difference between properties of beta receptors in the heart and beta receptors in other tissues has important clinical implications since it should permit the development of pharmacological agents to specifically stimulate or block the cardiac beta receptor without affecting other tissues At present there are several agents which show a relatively greater specificity for interacting with $beta_1$ receptors than with beta receptors [1]

Binding of catecholamines to the beta receptor triggers a series of reactions which eventually lead to the physiologic response The exact nature of these reactions is uncertain but it has been suggested that the formation of cyclic adenosine monophosphate (cAMP) may be the link between beta receptor stimulation and the response of the target organ Studies of a variety of tissues have shown that beta receptor stimulation increases the activity of the membrane bound enzyme adenylate cyclase Adenylate cyclase then catalyzes the formation of cAMP from ATP [10] The sequence of events can be prevented by beta receptor blockade The exact manner by which the formation of cAMP causes the subsequent physiological reaction is uncertain but some possibilities are discussed in a later section Caution must still be applied in interpreting the experimental evidence however as the increase in cyclic AMP levels which results from beta re

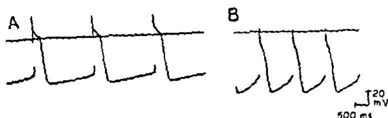


Fig 2 Catecholamine induced spontaneous activity in a canine Purkinje fiber (*Panel A*) and in a human specialized atrial fiber (*Panel B*) Norepinephrine caused the appearance of spontaneous diastolic depolarization in both fiber types (Adapted from Lefkowitz R J Isolated hormone receptors physiologic and clinical implications, N Engl J Med 288 1061 1973 Reproduced by permission)

ceptor activation may not be causally related to the physiological response

III The effects of beta adrenergic stimulation on normal cardiac cellular electrophysiology

Cardiac beta adrenergic receptor stimulation either by norepinephrine released from intrinsic cardiac sympathetic nerves or by exogenously administered catecholamines elicits a wide variety of electrophysiological responses in different fibers Such stimulation also results in positive inotropy Recent studies have also indicated that some electrophysiological responses to catecholamines are mediated by alpha receptor stimulation However unless we specifically indicate that a response is due to alpha receptor stimulation it can be assumed that it results from activation of beta receptors.

Sinus node The action potentials of pacemaker cells within the sinus node show marked spontaneous diastolic (phase 4) depolarization which proceeds to threshold potential initiating the regenerative depolarization phase of the action potential Sympathetic stimulation or catecholamines predominantly increase the slope of phase 4 depolarization (accelerate the decline in membrane potential from maximum diastolic to threshold potential) and thereby shorten the cycle length between spontaneous action potentials There is little consistent effect on maximum diastolic potential although it may be increased slightly If this does occur it probably is not sufficient to affect spontaneous firing rate

The effect of catecholamines on threshold potential of sinus node fibers is also uncertain and does not explain the acceleratory effects of catecholamines on impulse initiation An increase in rate of rise of phase 0 depolarization and overshoot of the sinus node action potential also occur as a consequence of catecholamine action It is uncertain whether this represents a direct effect on the magnitude of inward current during the action potential or is secondary to the enhanced phase 4 depolarization, in sinus node fibers unlike Purkinje fibers enhancing phase 4 depolarization may *increase* V_m and amplitude of the action potential upstroke[1]

An additional effect of symphathetic nerve stimulation is to shift the pacemaker site within the sinus node[13] This may be a consequence of the uneven distribution of nerve fibers within the node Sympathetic activation may result in greater increase in local concentration of norepinephrine in some regions of the node more than in others enhancing phase 4 depolarization more in some nodal fibers than in others and causing a shift in the pacemaker site to the nodal fibers which have the greatest response A second possible mechanism for the pacemaker shift is that some sinus node fibers may be more sensitive to the actions of catecholamine than others although this has not been proved

Atrium Beta adrenergic receptor stimulation has little effect on the action potential of working atrial myocardium Catecholamines may accelerate slightly the time course of repolarization in some species (dog cat) and prolong it in others (rabbit guinea pig rat) Part of this effect may be due to stimulation of alpha adrenergic receptors[1] Catecholamines in high concentrations accelerate repolarization of normal human working atrial myocardial cells When resting membrane potential and V_m of phase 0 are within the normal range catecholamines do not affect these electrophysiological parameters

Catecholamines and presumably sympathetic stimulation do have significant effects on specialized atrial fibers located in the crista terminalis Such fibers have Purkinje like action potentials there is a significant plateau phase

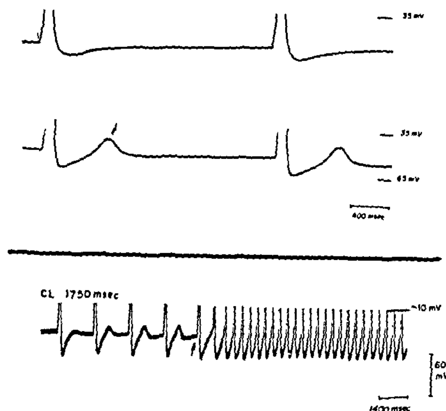


Fig 3 Effects of catecholamines on action potentials of cardiac fibers in the mitral valve leaflet of the monkey The top panel shows control recordings Only the bottom part of the action potential is displayed Note that the fiber repolarizes to a membrane potential which is more negative than the membrane potential at which the upstroke is initiated and then membrane potential gradually declines The middle panel shows the effects of 1 μg/ml epinephrine The catecholamine has elicited a delayed after depolarization (*arrow*) which does not result in a regenerative action potential The bottom panel demonstrates the effects of decreasing stimulus cycle length on the amplitude of the catecholamine induced after depolarization The stimulus cycle length was abruptly decreased from 2500 msec (not shown) to 1750 msec At this stimulus cycle length the amplitude of the after depolarization gradually increased (*first 4 action potentials*) After the fifth stimulated action potential (*arrow*) the after depolarization reached threshold and continuous spontaneous activity occurred

during repolarization and these cells may develop spontaneous diastolic depolarization [16] Beta adrenergic stimulation results in the appearance of spontaneous diastolic depolarization in fibers which do not demonstrate this phenomenon prior to stimulation or enhances the slope of phase 4 depolarization in fibers in which it is present prior to catecholamine administration (Fig 2) As a result, these atrial fibers may spontaneously initiate action potentials and function as pacemaker cells [1]

Catecholamines also enhance pacemaker activity in atrial fibers in the mitral valve leaflet [17] This effect is exerted by a mechanism differing from that which occurs in the atrium or sinus node Catecholamines initiate a delayed afterdepolarization in mitral valve fibers the amplitude of which is rate sensitive (Fig 3) In the presence of catecholamines an increase in the rate at which mitral valve fibers are stimulated results in an increase in the amplitude of the catecholamine induced delayed afterdepolarization until it reaches threshold at which time spontaneous action potentials occur [1] The mitral valve leaflets are richly innervated with adrenergic fibers indicating that these effects may occur *in situ* as well as *in vitro* [18]

Atrioventricular (AV) node Beta adrenergic receptor stimulation improves or speeds impulse conduction through the AV node The exact cellular effects of catecholamines which cause this response have not been studied in detail due to the technical difficulties of maintaining action potential recordings from single nodal fibers during exposure to catecholamines Nevertheless some data are available Electrophysiologically the AV node is composed of several different regions each of which has its characteristic action potentials Fibers in the upper (AN) region have low maximum diastolic potentials and action potentials with a slow upstroke which may have several notches and a low amplitude Much of

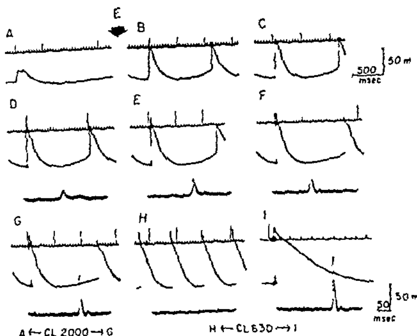


Fig 4 Catecholamine induced hyperpolarization of a canine Purkinje fiber Panel A shows the transmembrane action potential recorded from an electrically stimulated Purkinje fiber with a low resting potential (approximately −65 mV) At this membrane potential the Na carrier system is mostly inactivated and therefore upstroke velocity is low and the cell does not depolarize to positive potentials (top trace = 0 potential) Epinephrine was added to the perfusion fluid between panels A and B at the arrow In panels B through G resting membrane potential velocity and amplitude of depolarization all increase as a result of the epinephrine effect The increase in upstroke velocity is indicated on the bottom trace of panels D to G by the height of the differentiated signal of the upstroke velocity In panel H the rate of electrical stimulation is increased and in panel I the Purkinje fiber action potential and the differentiated signal of the upstroke velocity are displayed at a more rapid sweep speed Epinephrine has restored a normal looking action potential (Compare panels A and I) From Singer D H, Lazzara R and Hoffman B F Interrelationships between automaticity and conduction in Purkinje fibers Circ Res 21 530 1967 Reproduced by permission of the American Heart Association)

the AV nodal conduction delay occurs in this region and the notches on the action potential upstrokes may signify a multiphasic input to these cells from the atrium The most significant effect of catecholamines is to increase the rate of rise of phase 0 depolarization and the action potential overshoot of these upper nodal cells without affecting resting membrane potential The notches on the upstroke of the action potential disappear Catecholamines may also increase the upstroke velocity of action potentials of cells in the midregion (N) of the AV node without changing maximum diastolic potential Conduction time through the upper and mid AV node is markedly enhanced (Klein and Wit unpublished observations) Cells in the lower region of the AV node (NH) have higher maximum diastolic potentials and action potentials with higher upstroke velocities and amplitudes than upper and mid nodal cells These transmembrane potentials are not affected by catecholamines (Klein and Wit unpublished observations)

Certain AV nodal cells may be capable of spontaneous impulse initiation This property is most likely confined to the fibers in the lower nodal region which may be a type of transitional fiber between the node and His bundle Catecholamines may enhance spontaneous diastolic depolarization and impulse initiation by these fibers

Ventricular specialized conducting system Beta receptor stimulation has no direct effects on the resting potential V_m of phase 0 or overshoot of normal Purkinje fibers There is no effect on membrane responsiveness Conduction velocity of basic or premature impulses is not affected Beta adrenergic receptor stimulation accelerates repolarization of the Purkinje fiber action potential and shortens action potential duration This effect is seen after perfusion with isoproterenol which stimulates only beta receptors Beta

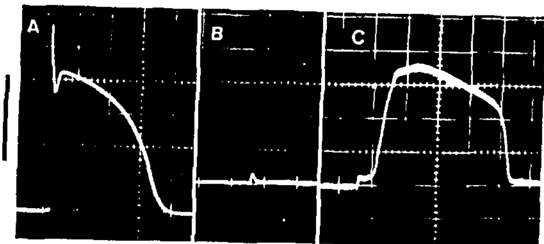


Fig 5 Effect of epinephrine on K depolarized bovine Purkinje fiber *Panel A* shows the control action potential *Panel B* shows the effect of increasing [K] in the perfusate from 4 0 mM in the control to 16.2 mM At 16 2 mM [K] the fiber has depolarized by 20 mV the fast inward current is inactivated only a small non propagated response is elicited by an extracellular stimulus *In panel C* 11 × 10 M epinephrine has been added to the high [K] perfusate Now a regenerative action potential with a slow rate of depolarization and a prolonged duration is initiated by the extracellular stimulus The action potential is a slow response elicited by the catecholamine Vertical calibration = 60 mV (from Carmeliet E and Vereeke J Adrenaline and the plateau phase of the cardiac action potential importance of Ca Na and K conductance Pfluegers Arch 313 300 1969 Reproduced by permission of the publisher)

receptor stimulation also increases the amplitude of the secondary depolarization or plateau in Purkinje fibers making it more positive [21] Norepinephrine which probably stimulates both alpha and beta receptors in the heart, slightly prolongs repolarization but this effect may be due to alpha receptor stimulation which overwhelms the beta adrenergic effect In the presence of alpha adrenergic blockade the effects of beta receptor stimulation by norepinephrine become apparent and action potential duration shortens

Beta receptor stimulation enhances spontaneous diastolic depolarization in Purkinje fibers, either inducing or increasing the frequency of spontaneous impulse initiation by these cells (Fig 2)

Ventricular muscle Beta adrenergic receptor stimulation has very little effect on the normal ventricular muscle fiber transmembrane potential Resting membrane potential V_m of phase 0 action potential amplitude, and conduction velocity are not influenced Repolarization may be either slightly accelerated or prolonged [14, 16] Spontaneous diastolic depolarization and automatic impulse initiation are not induced [14]

IV The effects of beta adrenergic stimulation on cellular electrophysiology of partially depolarized cardiac fibers

The electrophysiological effects of catecholamines on cardiac fibers with abnormally low resting or maximum diastolic membrane potentials are different from the effects of catecholamines on normal fibers The type of effect which occurs is dependent on the specific cause for the loss of resting membrane potential

In vitro studies of isolated, superfused atrial ventricular and Purkinje fibers which have low membrane potentials due to mechanical trauma anoxia or cold have demonstrated that catecholamines can restore the resting membrane potential to more normal values (hyperpolarization) (Fig 4) [1, 4] Cardiac fibers with low resting potentials have low V_{max} of phase 0 action potential amplitude and a slow conduction velocity The catecholamine induced increase in resting potential results in an increase in V_m of phase 0 action potential amplitude and conduction velocity (Fig 4) since more Na channels are available at the higher level of membrane potential It is possible that catecholamines may convert slow response action potentials to fast responses by this action if prior to catecholamine administration resting potential is low enough to inactivate all the fast channels leaving only the slow channels available Hyperpolarization would restore the fast response In such partially depolarized Purkinje fibers catecholamines also may abolish spontaneous diastolic depolarization and automatic impulse initiation rather than induce it Purkinje fibers with low maximum diastolic potentials may be automatic as a result of the pacemaker mechanism manifested when membrane potential is less than about −60 mV The

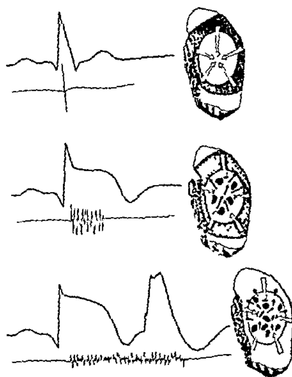


Fig 6 Possible mechanism for catecholamine induced reentry in ischemic or infarcted ventricular muscle Left panels show ECG and bipolar electrograms recorded from an ischemic intramural site in the left ventricle Diagrams at the right show the ischemic region of the left ventricular wall enclosed by the circle and the pattern of activation by a propagating impulse indicated by the arrows At the top within minutes after the onset of ischemia before the ST segment becomes elevated on the surface ECG the amplitude of the bipolar electrogram decreases from the control (*which is not shown*) but it is still a uniform deflection which lasts for only about 10 msec At this time the ischemic region may be activated as shown to the right impulses propagating into this region (*indicated by arrows*) from all the borders may collide and die out Other sequences of activation are also possible In the center after several more minutes have progressed there is elevation of the ST segment in the ECG The bipolar electrogram has declined in amplitude is fragmented and electrical activity persists for over 100 msec but does not extend past the end of the T wave The change in characteristics of the bipolar ECG may be due to the events depicted at the right Unidirectional conduction block has developed at the upper border of the ischemic area preventing impulses (*arrows with horizontal lines*) from propagating into the infarct in these regions However impulses still enter the ischemic region from the lower border (*open arrows*) and conduct slowly to the opposite border through the dead and dying tissue (*solid arrows*) The impulse conducting through the ischemic area arrives at this upper border while the surrounding normal tissue is still absolutely refractory (*dark shading*) and cannot reexcite the heart At the bottom after several more minutes have progressed the bipolar electrogram has declined further in amplitude is even more fragmented and electrical activity in the ischemic region persists beyond the end of the T wave on the ECG Such electrical activity is associated with a ventricular premature contraction This may be due to the events shown at the right Now there is still unidirectional block along the upper border for impulses attempting to invade the ischemic region (*arrows with horizontal lines*) The impulses entering the ischemic area from the lower border conduct even more slowly through this region (*solid arrows*) and reach the upper border after surrounding normal tissue has recovered excitability (*light shading*) and now may propagate out to reexcite the heart as a premature depolarization. The slow conduction and unidirectional block in ventricular muscle which is necessary for reentry may result from the elevated [K] and catecholamines in the ischemic region (Modified from Boineau J P and Cox J L Slow ventricular activation in acute myocardial infarction A source of reentrant premature ventricular contractions, Circulation 48 (0? 19?3 by permission of the American Heart Association)

increase in membrane potential caused by catecholamines inactivates this mechanism

If the membrane potential of cardiac fibers is low as a result of an elevation in $[K]_o$ the effects of catecholamines are quite different When $[K]_o$ is about 16 mM membrane potential of atrial ventricular or Purkinje fibers is reduced to around −60 mV the fast sodium system is inactivated and fast responses cannot be elicited The high K conductance (g_K) which is present when $[K]_o$ is elevated also prevents the occurrence of action potentials due to the slow inward current The slow inward current is insufficient for generating an action potential in the face of the increased outward K current [3] Exposure of these cardiac fibers to catecholamines enables action potentials to be generated in the presence of the elevated $[K]_o$ without affecting the resting membrane potential [29] The resultant action potentials have very slow depolarization phases (<5 V/sec) and conduct extremely slowly (<0 1 m/sec) (Fig 5) The catecholamines exert this effect by shifting threshold potential for slow current activation to more negative values and by increasing the magnitude of the slow inward current [3]

V Mechanisms of catecholamine effects on cardiac electrophysiology

Catecholamine stimulation of the cardiac beta adrenergic receptor appears to be the first step which in turn may elicit several electrophysiological effects by different mechanisms Catecholamines induce or enhance pacemaker activity in several different types of cardiac fibers The mechanism for this effect has been most thoroughly studied in Purkinje fibers where the ionic

mechanisms for spontaneous diastolic depolarization are to some extent known The pacemaker potential in these fibers occurs as a result of a decline in a slow outward K current (i_{K_2}) during diastole i_{K_2} is maximally activated during the plateau phase of the action potential (at −60 mV) and repolarization to around −90 mV causes its deactivation and a slow decay of net outward current A steady inward current probably carried by Na ions in combination with this fall in outward current produces the pacemaker depolarization [30] Catecholamines accelerate pacemaker activity in Purkinje fibers by a selective effect on the kinetics of i_K they cause a more rapid and complete deactivation of i_K at any given potential in the diastolic voltage range at which it is present (−90 to −60 mV) This results in a more rapid decline in the outward K current Catecholamines do not increase the inward Na current nor directly alter the threshold for activation of the fast Na current [30]

It has been suggested that the catecholamine induced displacement of voltage dependent kinetic parameters for i_{K_2} toward less negative potentials resulted from a direct alteration of the surface charge of the membrane near the i_{K_2} channel by the positively charged catecholamines [11] More recent studies however, have linked the increase in pacemaker potential to the activation of adenylate cyclase and an increase in intracellular cyclic AMP [3, 31] The exact manner in which such an increase in cyclic AMP can affect the i_{K_2} channels and enhance spontaneous diastolic depolarization is unknown, but two theories have been postulated Tsien and colleagues[33] have suggested that cyclic AMP may activate a protein kinase which brings about phosphorylation of the inside of the membrane near the i_{K_2} channel McNaughton and Noble[34] propose that a cyclic AMP activated protein kinase results in an increase in calcium uptake by the sarcoplasmic reticulum and thereby the removal of Ca from specific binding sites near the channel This would change the voltage gradient across the channel, making it more negative inside Such a change would tend to inactivate it more at each level of membrane potential The catecholamine effect on the i_{K_2} channel is saturated at very low levels of catecholamine (10^{-6} M epinephrine), a concentration which does not saturate the other electrophysiologic effects [33]

A second important effect of beta adrenergic receptor activation by catecholamines is on the membrane channel through which the slow inward current passes Catecholamines shift the threshold for activation of the slow channel to more negative potentials and increase the density of the slow inward current [35, 36] Some evidence suggests that this also may result from an increase in cyclic AMP concentration [114, 37] Higher concentrations of catecholamines are required to exert a maximal effect on the slow channels than on the channels responsible for the pacemaker potential These effects on the slow inward current probably explain the effect of catecholamines on the plateau of Purkinje fibers,[35] on the rate and amplitude of depolarization of AV nodal cells, and on action potential initiation in Purkinje fibers partially depolarized by high [K] [38]

The third important effect of beta receptor stimulation is an increase in activity of the active ion transport Na-K pump [2] This increase in activity results in an increase in transport of K into the cell and an increase in Na transport out of the cell This is particularly important in cardiac fibers with depressed Na-K transport in which a loss of $[K]_i$ and an increase in $[Na]_i$ has resulted in partial depolarization Catecholamines can increase resting membrane potential in these fibers by increasing pump activity [39] This effect on the pump can also suppress spontaneous diastolic depolarization [40]

VI Electrophysiologic effects of beta receptor stimulation on the in situ heart

Most of the effects of beta receptor stimulation on electrical activity of the in situ heart can be explained in terms of the actions of catecholamines on the transmembrane potentials just described The increase in sinus rate which is one of the most prominent responses to sympathetic stimulation needs no additional explanation Sympathetic stimulation has no significant effects on conduction or refractoriness of the atria However, since atrial muscle has both alpha and beta receptors endogenously released norepinephrine probably activates both The effects of pure beta receptor stimulation can only be determined after alpha receptor blockade and this experiment has not been reported

Beta receptor stimulation has prominent effects on conduction and refractoriness of the AV node Conduction velocity is increased and

both the functional and effective refractory periods of the AV node are decreased when the sympathetic nerves are activated [41,43] The number of impulses which can successfully traverse the AV node per unit time is thereby increased The increase in AV nodal conduction velocity can be seen as a shortening of the A H interval of the His bundle electrogram or the PR interval on the surface ECG [4] The shortening of the refractory periods may be manifested as an increase in ventricular rate during rapid atrial rhythms with AV block due to a lessening of the degree of block

Beta receptor stimulation usually has no effect on conduction in the ventricular specialized conducting system but may slightly shorten the relative refractory period [5] Catecholamine administration may occasionally accelerate conduction but this effect probably results from the release of K from the liver [4] Stimulation of cardiac sympathetic nerves does not have this effect There is no change in the H V interval on the His bundle ECG Pacemaker effects are discussed in more detail below

Sympathetic stimulation does not significantly affect conduction in ventricular muscle but it does shorten the effective refractory period Sympathetic stimulation also can result in changes in the wave form of the S T segment and T wave on the ECG and these changes probably result from alterations in the ventricular muscle action potential The type of change which occurs in the T wave is dependent on whether all the sympathetic nerves to the ventricles are activated or only individual nerves to limited regions of the ventricles are activated In experimental studies on the canine heart bilateral stellate ganglion stimulation does not produce marked changes in the T wave or ST segments a small increase in T wave amplitude can occur [6] In contrast left stellate ganglion stimulation alone results in a marked increase in T wave amplitude and a prolongation in the QT interval in the appropriate ECG leads Similar effects occur after right stellectomy indicating that the imbalance between the right and left side is the important factor in producing these ECG changes Vincent Abildskov and Burgess have postulated a mechanism for these electrocardiographic effects They have estimated that over 90 per cent of the body surface ECG manifestations of ventricular recovery are cancelled due to opposing wave fronts Stimulation of the left stellate shortens repolarization time and refractoriness of ventricular muscle on the posterior surface of the heart and therefore QT prolongation might seem paradoxical However the localized shortening of recovery properties may permit areas previously cancelled to contribute to the T wave The converse is also theoretically possible prolongation of the recovery time in critical areas due to a decrease in sympathetic activity could result in cancellation of the effects of areas contributing to the terminal portion of the T wave and thereby shorten the QT interval Notched T waves also may result from unilateral sympathetic activation due to an increased disparity in recovery times between two areas of the ventricle Changes in ST or T waveforms may be clinical manifestations of alterations in sympathetic activity Congenital prolongation of the Q T interval may result either from decreased activity in the right sympathetic nerves or an abnormal increase in the left T wave changes also commonly accompany central nervous system abnormalities due to cerebrovascular accidents head trauma tumors or infections [5]

Stimulation of the cardiac sympathetics may cause a small decrease in the diastolic threshold of ventricular muscle The mechanism for this effect is unknown [7]

The effects of beta receptor stimulation due to sympathetic nerve activation on ventricular vulnerability is different from the effects of catecholamine infusion on ventricular vulnerability Catecholamine infusion results in an initial slight increase in vulnerability (a decrease in fibrillation threshold) followed by a decrease in vulnerability [5] On the other hand sympathetic nerve stimulation increases ventricular vulnerability [51,52] The difference in the effects may result from the inhomogeneous distribution of the sympathetic nerves stimulation of which may cause dispersion of refractoriness in the ventricles and reentry (see below) Catecholamine infusion does not produce dispersion of refractoriness [52]

VII Electrophysiologic effects of beta receptor stimulation on the in situ heart Mechanisms for cardiac arrhythmias resulting from sympathetic activation

Activity of cardiac nerves may cause a variety of arrhythmias Arrhythmias may result from the influences of a normal sympathetic nervous sys

tem on hearts without disease The origin of these arrhythmias which are probably unimportant clinically can be explained by *the effects of catecholamines on normal cardiac fibers* The more serious clinical cardiac arrhythmias caused by *the sympathetic nervous system probably result from abnormalities in sympathetic influences on the heart* *These may result from* abnormally high activity in cardiac sympathetic nerves abnormalities in distribution patterns of the cardiac sympathetic nerves over the heart or abnormalities in the responsiveness of myocardial fibers to catecholamines which may be caused by cardiac disease *Other factors also may be involved* Examples of some of these are included in the following discussion

Arrhythmias due to alterations in automaticity The enhancement of spontaneous diastolic depolarization in pacemaker and latent pacemaker fibers by catecholamines has been described A generalized activation of the cardiac sympathetics in the normal heart usually causes a greater increase in automaticity of the normal SA nodal pacemaker than automaticity of latent ectopic pacemakers and therefore any increased tendency for ectopic pacemaker firing will be suppressed by sinus node overdrive Sinus tachycardia is therefore usually the normal response to factors such as exercise or emotion and may become a clinical problem only if there are abnormally high or persistent levels of sympathetic activity following normal physiological stimuli

The different cardiac sympathetic nerves innervate different regions of the heart and they may be activated individually instead of in a generalized manner Enhanced sympathetic activity to latent pacemaker sites might occur in the absence of increased activity to the sinus node and result in ectopic atrial or ventricular impulse initiation The distribution of the nerves which are activated would determine the type of arrhythmia Although atrial and ventricular ectopic beats may occur in normal hearts after physiological stimuli which activate the sympathetic nervous system atrial or ventricular tachycardias are less frequent and may result from discrete sympathetic influences on ectopic pacemakers

An asymmetry in the sympathetic effects on the heart resulting in cardiac arrhythmias similar to those resulting from localized nerve activation also may result from an enhanced responsiveness to catecholamines in some regions of the heart but not others, due to underlying cardiac pathology For example Purkinje fibers *in the normal canine ventricle* rarely initiate impulses at rates greater than 60 to 100 per minute after maximum sympathetic activation These rates are usually still slower than the sinus rhythm, and therefore ventricular tachycardias resulting from enhanced automaticity due to sympathetic discharge are rare in normal hearts This is probably true in humans as well Purkinje fibers in canine infarcts however may respond to sympathetic stimulation with automatic impulse initiation at much higher rates resulting in ventricular tachycardias Digitalis also may enhance the actions of catecholamines on Purkinje fiber automaticity causing ventricular arrhythmias Enhanced responsiveness of cardiac fibers to catecholamines also may result from other, as yet unknown causes Such abnormal responsiveness also might occur in different regions of the atrium and cause tachycardias here or even in the sinus node

Any influences that depress normal pacemaker function simultaneously with activation of cardiac sympathetic nerves also can cause arrhythmias Sinus node disease might prevent a normal response of the sinus node to sympathetic activation but not influence the response of ectopic pacemakers Simultaneous activation of parasympathetics and sympathetics results in inhibition of the sinus node and other supraventricular and junctional pacemakers which are responsive to acetylcholine and enhancement of ventricular pacemakers which are largely insensitive to acetylcholine

Arrhythmias due to reentry Cardiac arrhythmias resulting from sympathetic effects on the heart also may result from reentry and several different mechanisms may be involved Reentry may result from the effects of the sympathetic nervous system on refractoriness of ventricular muscle Catecholamines may moderately shorten action potential duration of ventricular muscle fibers In the *in situ* heart with nonuniform distribution of ventricular sympathetic nerve endings (i e some ventricular fibers may be surrounded by a large density of nerve endings while others are in sparsely innervated regions) sympathetic activation may result in a nonuniform decrease in the refractory period The refractory period may become shortened in

some fibers but remain unaltered in other fibers which might be in an adjacent region Also activation of individual sympathetic nerves rather than the entire sympathetic supply to the ventricles would have similar selective effects on refractoriness since different relatively discrete regions of the ventricle are innervated by different sympathetic nerves According to Han and Moe[61] the resultant nonuniform decrease (dispersion) in refractoriness may predispose to reenty Reentry might occur during sympathetic activation if an early ectopic impulse is generated in the ventricle (perhaps as the result of the sympathetic induced spontaneous diastolic depolarization in a Purkinje fiber) This ectopic impulse would propagate along an irregular wave front since it would encounter myocardial cells in various states of excitability Conduction initially would block in regions of the ventricle where refractoriness was not greatly altered by sympathetic discharge but might proceed through regions where the refractory period was shortened The conducting impulse would return to excite the region of myocardium in which it initially blocked A functional reentrant pathway might be established and reentry perpetuated resulting in ventricular tachycardia or fibrillation This may be one means by which sympathetic activation can decrease the fibrillation threshold The effects of sympathetic activation on dispersion of refractoriness might be potentiated by underlying pathology Myocardial ischemia may result in even greater local differences in the refractory period after sympathetic discharge than in the normal heart and a greater tendency for the heart to fibrillate Thus may be a way by which the sympathetic nervous system precipitates severe ventricular arrhythmias shortly after coronary occlusion The validity of this postulate concerning the role of a dispersion of refractoriness of ventricular muscle resulting from sympathetic stimulation as a cause of reentry however is still subject to debate since the quantitative differences in refractoriness in different regions of the ventricle are usually small and it is uncertain whether they would permit reentry to occur

Reentry due to dispersion of refractoriness has been postulated to be a cause of ventricular fibrillation s ncope and death in patients with congenital Q T prolongation A relative imbalance in sympathetic activity of unknown origin between the cardiac nerves emanating from the right and left stellate ganglia has been demonstrated to cause Q T prlongation in experimental animals and in some humans * This imbalance also could cause differences in refractoriness in different regions of the ventricle leading to arrhythmias

With the proper conditions sympathetic activation also might elicit slow response action potentials and cause reentry to occur by the mechanism of slow conduction and unidirectional block After an acute coronary artery occlusion ventricular muscle cells deprived of their source of oxygen and nutrients begin to leak K into the extracellular environment This is due to alterations in membrane permeability and decreased function of the Na-K pump The increase in [K]o may depolarize ventricular muscle cells in infarcting and adjacent regions Subendocardial Purkinje fibers adjacent to infarcting ventricular muscle also would be depolarized[62] It can be envisioned (although direct experimental evidence is lacking) that [K] may be so high that the decrease in resting membrane potential which it causes completely inactivates the fast inward Na current in some fibers and they become inexcitable Under these conditions catecholamines released locally from sympathetic nerve endings might cause slow response action potentials to appear by the mechanism described above Slow response action potentials in ventricular muscle cells in or adjacent to the ischemic or infarcted region or in subendocardial Purkinje fibers would result in reentrant excitation (Fig 6) Similarly slow response action potentials might result from sympathetic stimulation of regions of myocardium in either atria or ventricles that have low membrane potentials due to other diseases

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Right ventricular monophasic action potential in patients with signs of digitalis overdosage

The suction technique of recording monophasic action potential (MAP) from the intact human heart due to its simplicity and the similarities between a MAP and an action potential (AP) recorded with microelectrodes in the close vicinity of each other appears valuable for the study of cellular repolarization phenomena[1]

A shortening of right ventricular monophasic action potential (RVMAP) after digitalis therapy in spite of decreased heart rate was reported by Olsson and Shabetai Suriwicz and Hammill Rosen Gelband and Hoffman have shown in early digitalis toxicity a shortening of AP duration and a decrease in its amplitude

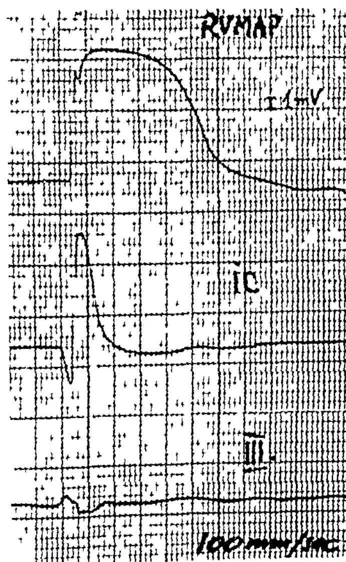


Fig 1 Simultaneous recording of right ventricular monophasic action potential (RVMAP) intraventricular electrogram (IC) and Lead III of a standard ECG in a patient with coronary heart disease and atrial fibrillation Right ventricular monophasic action potential duration extrapolating phase 3 repolarization is 290 msec Paper speed is 100 mm per second

The purpose of this paper is to analyze the RVMAP obtained by a suction electrode technique [4] in patients with digitalis overdosage

Using a simple bedside technique with bipolar electrode catheters and suction we were able to record the RVMAP in all patients The technique is a percutaneous one through a brachial vein similar to the flow-directed catheter technique and locating the catheter in the right ventricle is performed under continuous monitoring of intracavitary electrograms recorded through the same catheter Once the catheter is placed in the right ventricle using negative pressure the tip of the catheter will suck against the endocardium wall and MAP is recorded[5] The RVMAP recorded in a patient with atrial fibrillation and coronary heart disease is presented (Fig 1)

Six males and nine females ranging in age from 36 to 72 years were studied All but one of the patients were in atrial fibrillation two patients with mitral valvular disease and the other patients with coronary heart disease All of the patients were treated with digitalis before the examination with evident signs of digitalis overdosage

We have paid attention only for the duration of RVMAP which was measured on the baseline in at least 10 consecutive complexes The RVMAP durations were between 220 and 370 msec and the mean duration was 277 ± 51 msec shorter than the mean RVMAP duration found by us in a former study in 31 normal subjects where RVMAP duration was 32? ± 37 msec

The duration of MAP is usually considered as having the closest correlation with the transmembrane action potential and provides information about the refractory phase of the myocardium

The short RVMAP duration in patients with clinical and electrical signs of digitalis overdosage may indicate a decreased refractoriness of ventricular myocardium The refractory period of the cardiac muscle is an important determinant of the nature of response to a given stimulus, and re entry can be favored by a shortening of RVMAP duration This phenomenon may be one of the explanations of the high incidence of ventricular arrhythmias during digitalis overdosage

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Serum enzyme changes following coronary bypass surgery

The importance of serum enzyme level changes in evaluating myocardial damage following coronary bypass surgery has recently been the object of controversial reports In particular there is no agreement as to the role of surgical manipulations in determining postoperative enzyme increases This brief communication reports our results on a prospective study concerning this problem

Two groups of patients undergoing cardiac surg ry were studied Both groups had extracorporeal circulation following median longitudinal sternotomy Forty three patients undergoing valve surgery in the first three months of 1973 (20 patients undergoing aortic valve replacement [AVR] and 23 patients undergoing mitral valve replacement [MVR]) were used as a control group Sixty three patients undergoing coronary artery venous bypass in the first six months of 1973 formed the second group Electrocardiograph (ECG) tracings and serum glutamic oxaloaceti transaminase (SGOT) creatine phosphokinase (CPK) lactic dehydrog nase (LDH) hydroxy butyrate dehydrogenase (HBDH) and serum glutamic pyruvic transaminase (SGPT) determinations were obtained before surgery and on the first second third and fifth postoperative days

Control group Postoperatively two patients demonstrated ECG evidence of transmural myocardial infarction The peak values of postoperative enzyme changes in the control group are reported in Table I (mean ± S D)

In the AVR and MVR subgroups a significant ($p < 0.001$) increase in enzyme levels above the preoperative values was found Marked elevation of enzyme levels occurred in the two infarct cases. Furthermore there was a significantly lower increase in SGOT ($p < 0.005$) LDH ($p < 0.005$) HBDH ($p < 0.025$) and SGPT ($p < 0.050$) in the AVR patients as compared with the MVR patients This difference may be due to the clinical state of the MVR patients who undergo surgery following periods of heart failure often with variable degrees of cardiac cirrhosis These patients are therefore more likely to be exposed to the toxi effects of anesthesia

Thus, patients who undergo coronary surgery are considered as being more similar to AVR than to MVR patients regarding postoperative enzyme increases Based on this presupposition, peak enzyme values in patients undergoing aortocoronary bypass were compared with the mean peak enzyme levels in the AVR subgroup

No relation was observed between the duration of extracorporeal circulation or aortic clamping and peak enzyme values

Bypass group Six out of 63 patients showed ECG evidence of transmural myocardial infarction with significant ($p < 0.001$) and marked increases in serum enzyme levels above the mean of the AVR group (Fig 1)

In the 5 patients without significant changes in the QRS complex 46 patients showed only mild enzyme elevations and were considered to be free from myocardial damage In 39 of these patients all enzyme values were within the mean of the AVR group In the seven other patients only one of the enzymes was elevated but within two standard deviat ons.

Eleven patients had no postoperative QRS changes but had marked elevation of a single enzyme (greater than two standard deviations above th mean) or moderate elevation of several enzymes These patients are described as doubtful cases in Fig 1 Within this group of doubtful cases two recurrent enzymic patterns can be described Some patients showed elevations in SGOT LDH and HBDH in association with marked and progressively increasing SGPT changes usually in the first postoperative week only small increments of CPK were seen Other patients showed low SGPT values associated with moderate changes in all other enzymes In our opinion the former group may be the result of hepatic damage or marked hemolysis in the latter group myocardial damage may have occurred without any evidence of QRS changes

Table I

Subgroup	No patients	SGOT	CPK	LDH	HBDH	SGPT
AVR	19	3[illegible] ± 9	380 ± 2[illegible]6	5[illegible]6 ± 149	285 ± 7[illegible]	[illegible]1 ± 7
MVR	22	53 ± 27	407 ± 198	688 ± 138	342 ± 92	31 ± 3[illegible]
Infarcts	2	[illegible]40 ± 120	1,315 ± 7 6	2,783 ± 1 083	1,550 ± 550	106 ± 25
Normal values		≤ [illegible]0	≤ [illegible]0	≤ [illegible]00	≤ [illegible]00	≤ 20

Annotations

Right ventricular monophasic action potential in patients with signs of digitalis overdosage

The suction technique of recording monophasic action potential (MAP) from the intact human heart due to its simplicity and the similarities between a MAP and an action potential (AP) recorded with microelectrodes in the close vicinity of each other appears valuable for the study of cellular repolarization phenomena

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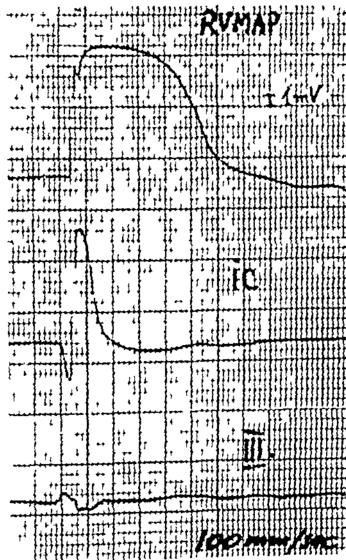


Fig 1 Simultaneous recording of right ventricular monophasic action potential (RVMAP) intraventricular electrogram (IC) and Lead III of a standard ECG in a patient with coronary heart disease and atrial fibrillation Right ventricular monophasic action potential duration extrapolating phase 3 repolarization [1] is 290 msec Paper speed is 100 mm per second

The purpose of this paper is to analyze the RVMAP obtained by a suction electrode technique[1] in patients with digitalis overdosage

Using a simple bedside technique with bipolar electrode catheters and suction we were able to record the RVMAP in all patients The technique is a percutaneous one through a brachial vein similar to the flow directed catheter technique and locating the catheter in the right ventricle is performed under continuous monitoring of intracavitary electrograms recorded through the same catheter Once the catheter is placed in the right ventricle using negative pressure the tip of the catheter will suck against the endocardium wall and MAP is recorded The RVMAP recorded in a patient with atrial fibrillation and coronary heart disease is presented (Fig 1)

Six males and nine females ranging in age from 36 to ?? years were studied All but one of the patients were in atrial fibrillation two patients with mitral valvular disease and the other patients with coronary heart disease All of the patients were treated with digitalis before the examination with evident signs of digitalis overdosage

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The short RVMAP duration in patients with clinical and electrical signs of digitalis overdosage may indicate a decreased refractoriness of ventricular myocardium The refractory period of the cardiac muscle is an important determinant of the nature of response to a given stimulus and re entry can be favored by a shortening of RVMAP duration This phenomenon may be one of the explanations of the high incidence of ventricular arrhythmias during digitalis overdosage

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Table I Modification of sexual activity after myocardial infarction

Frequency of intercourse	No of patients	
Unchanged	36	
Patients without sexual activity		15
Patients with sexual activity		21
Moderately diminished	33	
Strongly diminished	29	
No sexual activity postinfarction		19
Some sexual activity postinfarction		10
Slightly increased	2	
Total	100	

and fear of sudden death were the main reasons The patient s physician can play a major role in this field Extensive discussions with the patient and sometimes with his wife including frequent explanations and reassurance will help the patient to resume an active sexual life after a myocardial infarction This appears to be very important at the time where rehabilitation measures are attempting to provide the coronary patient with a completely normal life

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Table II Exercise tests and postmyocardial infarction sexual activity

Highest work load (watts) achieved during 5 minutes	No of patients	Monthly frequency of intercourse	
		Range	Mean
50	13	0-8	1 9
75	24	0-10	1 6
100	26	0-18	4 2
125	17	0-8	2 1
150	8	0-30	7 6
175	3	0-4	1 7

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Of being properly clothed

Infections, especially respiratory infections, are common precipitating causes of congestive and anginal heart failure and are even fatal complications of heart disease Respiratory infections are much more common in the winter than in the summer Every grandmother knows that people "catch colds when the weather changes to cold and wet and when people are not clothed warmly for these environmental conditions The main difference between the winter and summer weathers is temperature Heat loss and the physiologic changes related to cooling of the body are factors which predispose in part at least to upper respiratory tract infections (U.R I) and other respiratory infections. But, if the body were kept warm by means of adequate clothing at *all* times and not allowed to cool, then the microcosmos at the surface of the body would be the same in summer and winter and the incidence of respiratory infections should be reduced. It is obvious to everyone who observes people on the street that most people are not warmly clothed on cold days The micro climate (the climate next to the skin) should be tropical or subtropical, i.e warm and comfortable at *all* times Proper clothing should shield the surface of the body from winter weather and winter climate so that heat loss is at the same rate and has the same time course throughout the year Thus with proper clothing people would live in a tropical climate at all times. Were this the case would there be an increase in incidence of upper and lower respiratory tract infections during any one month of the year? Would influenza epidemics be reduced in number and severity? It is my opinion that U R I would be reduced markedly if summer weather existed (by means of proper clothing and housing) at *all* times for all people who live in the advanced nations of the world. The prevention of infections in all people and especially in those with cardiac disease would be extremely valuable for the health of man Patients with heart disease should be properly clothed and housed.

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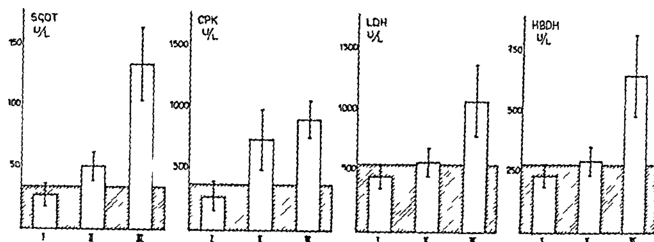


Fig 1 Peak enzyme changes after bypass surgery (mean ± S D) I patients free from myocardial damage (46 cases) II doubtful cases (11 cases) and III patients with transmural myocardial infarction (6 cases) Shaded areas show the mean peak enzyme values of the AVR control group

In conclusion a correct diagnosis of the surgical impact on the myocardium seemed to be feasible by routine enzyme determinations in at least 82 per cent of the patients In many cases enzyme changes simply help to confirm ECG data more importantly the possibility of significant myocardial damage can be excluded in several patients despite marked alterations in the ECG repolarization pattern

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Sexual problems after myocardial infarction

Sexual activity of postmyocardial infarction patients still represents a poorly known subject and very few publications have been devoted to it During a randomized study on early mobilization after acute myocardial infarction[1] we recently had the opportunity of studying the sexual evolution of a group of coronary patients One hundred patients were seen for an outpatient follow up examination on an average of 11 months after an acute myocardial infarction They were systematically questioned on their usual sexual activity before the infarction and at the time of the follow up examination This report deals with 88 males and 12 females the mean age was 58 years (28 to 71)

Table I shows that myocardial infarction causes an important diminution of the sexual activity The monthly mean frequency of sexual intercourse was 5 2 before the infarction and 2 7 only eleven months after the infarction This diminution was more marked in older patients but could be seen in all age groups. The important reduction of sexual activity is especially surprising if we consider the fact that almost all patients had resumed a normal active life Thus 89 per cent of the nonretired patients had returned to work Ninety one patients were given exercise tests with a bicycle ergometer Table II shows the absence of correlation between work capacity and frequency of intercourse Some patients with a high physical fitness had no more sexual activity others continued to have quite frequent intercourse in spite of a poor physical fitness

Reasons given by the patients to explain the reduction of their sexual activity were often unclear or multiple The main reasons were in decreasing frequency decrease in sexual desire depression anxiety wife's decision fear of relapse or of sudden death fatigue angina and impotence These explanations are close to those reported by Hellerstein and Friedman[2] On the other hand impotence which was seen in 10 per cent of the cases reported by Tuttle Cook and Fitch was mentioned only by one of our 100 patients

The main reason for the reduction of sexual activity after myocardial infarction appeared to be due to psychological factors We have found that in most of our patients signs of latent depression fear of relapse during sexual intercourse

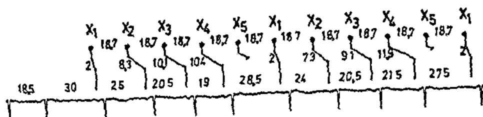


Fig 1 There are two consecutive groups of 5 4 SA Wenckebach conduction The second sequence is atypical. Intervals are measured in mm (5 mm = 1 sec) An assumption is made for the shortest SA conduction time after a long pause (? mm)

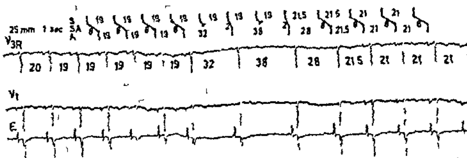


Fig 2 Concomitant first and second-degree SA block. Intervals are measured in mm (25 mm = 1 sec) An assumption is made for the shortest SA conduction time after a long pause (2 mm)

interval after a long pause is longer than the PP interval before The second sequence is atypical but calculation of sinus cycle yields the same value as obtained for the preceding typical Wenckebach period.

Fig 2 is an example of a concomitant first and Type 2 second-degree SA block All PP intervals are equal to corresponding RR intervals as there is no change in AV conduction Doubling of the PP interval from 19 to 38 mm is typical for a 2 1 second-degree SA block (Type 2) When there is 1 1 SA conduction the SA conduction time is lengthening The slight variation in P morphology after a long pause is due to intraatrial conduction disturbance

The differential diagnosis between sinoatrial block and sinus arrhythmia is always rather difficult. Nevertheless in this case the diagnosis of sinoatrial block seems very likely as there are acceptable arguments for both Type 1 and Type 2 second-degree sinoatrial heart block

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Fibrinogen and mural thrombosis

To the Editor

We were interested to read the report "The possible use of I labeled fibrinogen for the detection of mural thrombosis following myocardial infarction by Drs Warlow and Terry Our own investigations[1] led us to a different conclusion namely that the relative increase in precordial counts was due mainly to the collection of labelled fibrinogen/fibrin between the visceral and parietal layers of the pericardium This conclusion was strengthened by the operative finding of a thick layer of pericardial fibrin in one of our patients when his acquired ventricular septal defect was closed on the fourteenth day following myocardial infarction

The patients in our study all of whom survived showed no evidence of arterial embolization

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Letters to the Editor

Left ventricular function in diabetes mellitus

To the Editor

The article entitled "Preclinical abnormality of left ventricular function in diabetes mellitus" (AM HEART J 89 153 1975) was of especial interest because it corroborates our assumption as indicated in a paper entitled New type of cardiomyopathy associated with diabetic glomerulosclerosis published in 1972[1] that a myocardial disease found in diabetic patients need not be associated with disease of the major coronary arteries The alterations that have reportedly affected skin muscle[2] and kidney can logically be expected to contribute to the diffuse myocardial fibrosis and hypertrophy we observed Moreover the accumulation of acid staining mucopolysaccharide material in the walls of intramural coronary arterioles may implicate small vessel disease as the etiology of these changes

The impairment in myocardial function described by the authors would be the anticipated consequence of the aforementioned pathology

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Reply

To the Editor

We thank Dr Rubler for her comments concerning our article Preclinical abnormality of left ventricular function in diabetes mellitus by Ahmed Jaferi Narang and Regan

The conclusions of the retrospective study of four patients with diabetes reported by Dr Rubler are in general consistent with the reports of Ledet and Sohar and colleagues The former however emphasized that thickening of small intramural vessels was usually not associated with luminal narrowing in his series Since occlusive disease of small vessels has been reported in amyloid heart disease without symptoms or signs of ischemia and without confluent areas of fibrosis the significance of such luminal narrowing when present in the diabetic patient must be questioned Since the morphologic findings reported by Dr Rubler were not specific a possible role of chronic uremia is not readily excluded The finding of abnormal function in noncardiac diabetic patients without complications of uremia obesity hypertension etc supports the view of an extravascular abnormality of the myocardium in this disease

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An atypical sinoatrial Wenckebach phenomenon

To the Editor

We read with great interest the article by Denes and associates in the January issue of the JOURNAL (AM HEART J 89 26 1975) In our department we are surprised by the increasing incidence of sick sinus syndrome which accounts at this moment for 20 per cent of all pacemaker implantations As the diagnosis of sinoatrial (SA) block sometimes can be questionable there may in the future be some interest for atypical sinoatrial Wenckebach phenomena

This letter deals with an atypical 5 4 sinoatrial Wenckebach phenomenon which is considered by Denes and colleagues as a difficult diagnosis (*p 31 Clinical implications*) In our example however the disturbances in SA conduction could be inferred by applying certain formulas[1]

Figs 1 and 2 were recorded on two different days in a patient with symptomatic sick sinus syndrome

Fig 1 is an illustration of an atypical sequence of Type 1 (Wenckebach) second degree SA block following one with all the Wenckebach characteristics There are two consecutive groups of 5 4 SA Wenckebach conduction In the first sequence there is a progressive lengthening of SA conduction time progressive shortening of PP intervals and the PP

Book reviews

Physique Cardiovasculaire By G Duboucher Paris 19 4 Masson & Cie Editeurs, 464 pages

This is a very fine review of the physical and hemodynamic principles and forces related to the heart and circulation Those who have neglected to learn the forces involved in maintaining the circulation and the influence of gravity on the circulation will find this book to be extremely valuable The author clearly presents in French the hemodynamic principles related to the entire circulation Unfortunately those who wish to study the subject in greater detail will find the bibliography to be inadequate These principles have been amply discussed in the medical literature in the past and this book summarizes them very well The book should interest physiologists and physicians who are interested in hemodynamic phenomena of the circulation The book is highly recommended

Card ac Catheterization and Angiocard ography in Severe Neonatal Heart Disease By Michael T Gyepes M D and William R Vincent M D Springfield Ill 1974 Charles C Thomas Publisher 183 pages Price $14.50

This book as the title indicates is concerned with the study of patients with severe neonatal heart disease Doctors Gyepes and Vincent indicate their approach to the problems The methods they use in preparing patients for study are described in a lucid manner with reasons to support their practices The equipment, procedures and care employed with these delicate sick patients are emphasized The principles of management of these extremely hazardous diseases and studies are presented for the cardiac pediatricians and radiologists who study and care for patients with serious cardiac disease

Heart Disease and P egnancy By Paul Szekely and Linton Snaith Edinburgh and London 1974 Churchill Livingstone 217 pages Price $24 50

This book is briefly written and is concerned with an important much neglected problem in cardiology and obstetrics Unfortunately the authors have been concerned more with statistical material than with the more pragmatic clinical problems of how to manage the heart disease in pregnancy For example the precise treatment for a patient who is in acute pulmonary edema and in labor is difficult for physicians and obstetricians alike Furthermore what is done when a patient consults his physician at 6 to 12 weeks pregnancy and presents with Ebstein s disease? Or what are the recommendations for a patient who needs, for obstetrical reasons a Caesarian section and is in congestive heart failure from rheumatic heart disease with mitral stenosis? These and numerous other similar problems confront the cardiologist on whom the obstetrician depends for advice The type of anesthetics best for patients the handling of serious tachyarrhythmias during labor and many other situations have received little consideration by the authors whereas isolated reports of statistics have received considerable emphasis Nevertheless because of the lack of recent reports on this important subject cardiologists will find useful information in this book And as the authors have relied upon the book of Burwell and Metcalfe (19) extensively cardiologists will want to restudy that book even though it is over 15 years old Szekely and Snaith have written a useful small book. It is hoped the second edition will contain much more practical clinical therapeutic information and recommendations. Nevertheless this is a very good book for cardiologists internists and obstetricians

Card ac Mechanics Physiological Clinical and Mathematical Cons derations Edited by Israel Mirsky Ph D Dhanjoo N Ghista Ph.D and Harold Sandler M D New York, 1974 John Wiley & Sons Inc 490 pages

The fundamental function of the heart is mechanical i.e to pump blood around the body It is generally accepted that it is an unusually efficient and excellent pump one which man has not yet succeeded in duplicating The many contributors to this book have discussed the basic principles of cardiac mechanics including functional aspects of ultrastructural morphology The biochemical basis for contraction and the relationship of heart size to its work are among the many problems presented The mechanics for heart failure are also presented It is not made clear that although congestive heart failure resides in disease and malfunction of the heart many extracardiac factors are set into motion to produce the entire clinical picture This is a good book however It is provocative and clearly indicates many gaps in knowledge The methods used in studying heart size and the time courses of volume change and shape change are extremely crude both for clinical and experimental purposes An engineer of hydraulics and mechanics should find this book interesting The original data recordings and publications reveal many difficulties yet to be resolved concerning cardiac mechanics This is a good book for the bioengineer to launch his deliberations and studies

The Sick Sinus Synd ome By M Irené Ferrer M D New York, 1974 Futura Publishing Company Price $13 50

Dr Ferrer has produced an interesting and important book on an electrophysiologic syndrome which is fairly common and hazardous The book contains brief discussions of SA node (SAN) anatomy and normal and abnormal function There always are opinions that differ concerning any clinical or electrocardiographic problem For example the discussions on exit block on page 6 are quite arbitrary Even the precise definition of exit block seems to be loosely used in cardiology today Without more precise recording of electric activity within the SAN itself exit block becomes a state that is difficult to recognize from the electrocardiogram It is conceivable that concealed conduction can exist in the SAN The node must develop problems related to refractoriness The exact mechanisms by which the SAN generates impulses and fires are little understood. Furthermore it must be remembered that a tracing of intracellular action potential is obtained from an injured cell, a cell injured by the recording procedure A healthy living cell is an extremely delicate structure And what about the parts of the cells near the recording intracellular microelectrode? These are among the many interesting questions related to electrocardiography and the sick sinus syndrome (SSS) This is a highly recommended book written by a competent author who has been interested in SSS for some time Thoughtful reading of this book can be extremely stimulating The more thoughtfully the book is read the more questions come to mind especially present-day ideas of interpretation management and prognosis of SSS and the like Ferrer develops her book so nicely that studying it is satisfying and thought provoking

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Reply

To the Editor

Thank you for allowing us to comment on the letter from Dr Wray and Dr Maurer Regrettably we were not aware of their report in which they examined the ratio between precordial and blood radioactivity after the injection of I fibrinogen in patients with acute myocardial infarction This method of detecting an abnormal accumulation of fibrin within or around the myocardium may well have been more sensitive than ours It is however surprising that none of their patients were found to have an increase in the precordial/blood radioactivity due to fibrin deposition in mural thrombosis since this occurs in about 44 per cent of patients who die after acute myocardial infarction Their evidence is by no means absolutely conclusive since in only one of their five cases with raised precordial/blood radioactivity was there validation of the pericardial inflammatory exudate and in the other four they cannot state that mural thrombus was *not* present in addition to clinically apparent pericarditis They state in their letter that none of their patients died although in the discussion section of their paper they have a contradictory statement that the validity of their technique was obtained in two cases one at post mortem and one at operation " It is disappointing that no necropsy details were given in their case reports In our series there were fourteen patients with a pericardial friction rub and a normal decay in precordial radioactivity although the four patients with delayed decay also had pericarditis We can only repeat what we have already written and what Dr Wray and Dr Maurer must surely agree with and that is it cannot definitely be stated that the rising precordial radioactivity is not due to deposition of fibrin outside mural thrombus in for example the pericardial cavity or coronary artery thrombus

Our conclusions were not meant to be more than tentative and clearly further clinicopathological studies will be necessary to define the site of fibrin deposition which is responsible for the increased absolute precordial or precordial/blood ratio of radioactivity in some patients after acute myocardial infarction

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Book reviews

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Medical Examination Review Book By Louis F Grenzer M D Flushing New York 1974 Medical Examination Publishing Company Inc 136 pp Price $7 50

This compendium consists of eight sections one being an answer key This small book contains a wealth of information in the form of questions and answers These questions and answers are based upon the third edition of the book The Heart by J Willis Hurst et al Thus this latter book is the foundation of information for the knowledge required to answer the many multiple choice questions contained in the compendium The review book is an extremely useful publication for all who are preparing for the subspecialty boards in cardiology Obviously the candidates for the examination must also be acquainted with the current literature The questions stimulate the candidate to review cardiology in detail and to practically memorize the book by Hurst and associates A study of this review book would be a profitable learning experience

Books received

Fundamentals of Family Practice By Wilfred Snodgrass MD DNB ABFP Philadelphia 1975 F A Davis Company 640 pp $35 00

Recent Studies of Hypothalamic Function Edited by K Lederis and K F Cooper Basel Switzerland 1974 S Karger AG 434 pp $49 75

Practice of Surgery vol II Current Review By Walter F Ballinger MD and Theodore Drapanas MD St Louis 19 The C V Mosby Company 49_ pp Price $[illegible] 50

Prostaglandin Synthetase Inhibitors Their Effects on Physiological Functions and Pathological States Edited by Harry J Robinson PhD MD and John R Vane DSc FRS New York 19 4 Raven Press .84 pp Price $24 00

Radionuclide Scanning in Cyanotic Heart Disease By Gates, Springfield Ill 1974 Charles C Thomas Publisher 88 pp Price $15 00

Problem Oriented Medical Diagnosis Edited by H Harold Friedman and Papper Boston 1975 Little Brown & Company 411 pp Price $8 95

Current Concepts in Radiology vol II Edited by E James Potchem St Louis 1975 The C V Mosby Company 312 pp Price $35 00

Evaluation of Liver Function in Clinical Practice *Edited by* S O Waife MD Edward L Platcow PhD and C E Hammond, Indianapolis, 1974 The Lilly Research Laboratories

Announcements

Clinical application of intra aortic balloon pump

The University of Miami School of Medicine Division of Thoracic and Cardiovascular Surgery and Cardiology will present a symposium entitled Clinical application of intra aortic balloon pump on November 14 and 15 1975 The meeting will be held at the Americana Hotel 9701 Collins Ave, Bal Harbour Florida The symposium precedes the Annual Meeting of the Southern Medical Association at Miami Beach November 16 through 20 1975 and the Annual Meeting of the American Heart Association at Anaheim California November 17 through 20 1975

The course is designed to provide cardiologists cardiac surgeons and allied professionals with information on the newest developments in the area of treatment of shock and heart failure Practical aspects of intra aortic balloon pump and intra aortic balloon pump in cardiogenic shock and cardiac surgery patients will be stressed Fees are $140 (U S) for physicians in practice and $75 (U S) for physicians in training nurses, and technicians

For further information regarding this meeting please contact Division of Continuing Medical Education University of Miami School of Medicine P O Box 520875 Biscayne Annex Miami Fla 33152 Telephone (305) 547 6716

Cardiopathy of aging symposium

"Cardiopathy of Aging III (heart disease in the elderly patient) will be presented in Little Rock Arkansas March 18 and 19 1976 by the Veterans Administration University of Arkansas School of Medicine Council on Clinical Cardiology of the American Heart Association and the Arkansas Heart Association Information regarding this symposium may be obtained from J E Doherty M D Program Director Cardiopathy of Aging III 300 E Roosevelt Rd Little Rock Ark 72206

Lucien Dautrebande Foundation prize

The Fondation de Physiopathologie Professeur Lucien Dautrebande will award its next prize of about 500 000 Belgian francs during the year 1976 The prize will be awarded for a work on human or animal clinical physiopathology such work preferably having therapeutic implications

For further information about this prize please write to the office of the Foundation 35 Chaussée de Liège (5200) Huy Belgium Competing papers must be submitted before December 31, 1975

Eighth International Heart Congress

The International Study Group for Research in Cardiac Metabolism will sponsor the Eighth International Heart Congress in Tokyo Japan on May 27 through 29 1976 For information regarding the congress please write Dr Y Ito Congress Secretary Tokyo University Branch Hospital, Bunkyo-Ku, Mejirodai 3-28-6 Tokyo Japan or Dr N S Dhalla Professor of Physiology Faculty of Medicine University of Manitoba Winnipeg, Canada R3E OW3.

Mind body self regulation symposium

Biofeedback Meditation and Self Regulatory Therapies. a special weekend Symposium cosponsored by Albert Einstein College of Medicine and the Institute for the Study of Human Knowledge will be held at the Roosevelt Hotel New York City on November 22 and 23 1975 Leading researchers will review recent scientific developments in the self-control of psychophysiological processes and will assess the therapeutic applications of mind body self regulation in areas such as hypertension cardiac arrhythmias stress syndrome muscular rehabilitation and drug use Included in the program are Neal E Miller Ph D The Rockefeller University New York Herbert Benson M D Harvard Medical School Boston John V Basmajian M D., Emory University Atlanta Bernard T Engel Ph D Johns Hopkins University School of Medicine Baltimore Bernard C Glueck M D The Institute of Living Hartford Wolfgang Luthe M D The Oskar Vogt Institute Montreal Arthur K Shapiro M D The Payne Whitney Psychiatric Clinic New York Hospital and Robert E. Ornstein Ph.D University of California Medical Center San Francisco

Further information can be obtained from Dr Mel Roman Department of Psychiatry Albert Einstein College of Medicine 1165 Morris Park Ave Bronx N Y 10461 Telephone (212) 597 1000 ext. 201

Controversies in CHD

An intensive two-day symposium on Controversies in Congenital Heart Disease designed for cardiologists and cardiovascular surgeons will be presented October 10 and 11 1975 in the MHMC UCI Center for Health Education Long Beach California Fee is $125 00 For additional information please write Executive Secretary Center for Health Education 2801 Atlantic Ave Long Beach Calif 90801

American Heart Journal

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Editorial

The advantages of a vasospastic cause of myocardial infarction

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This editorial will renew the suggestion that it is likely myocardial infarctions are caused by vaso spasm a process which might be reversible If this is true proper and timely antispasmodic therapy might provide the most advantageous treatment for this disorder and ultimately infarctions might be prevented Such possibilities provide impetus for the clarification of any role of spasm in infarction

Practically all of the recent work in infarction has been in preserving ischemic myocardium (limiting infarction size) and improving hemodynamics after the acute attack [4] This school assumes that after an acute episode ischemic myocardium can be separated into two classes blighted myocardium where necrosis is inevitable and jeopardized muscle which can be preserved by techniques which improve the myocardial oxygen supply-demand ratio

Contrariwise there appears to be little interest in elucidating the pathogenesis of infarction In fact articles dealing with methods of improving the care of acute infarction generally skirt the issue of its pathogenesis It probably is understood that stenotic atherosclerosis causes myocardial ischemia but it is not always clear if it is assumed that this chronic arterial disorder is the proximal cause of the acute attack [1] If the acute episode is mentioned it often is styled as a "coronary occlusion" or "acute event" without further comment Possibly it is assumed that efforts to clarify the cause of the acute ischemia of infarction would be unrewarding and further it most likely represents an irreversible *fait accompli* (?stenotic atherosclerosis) which inevitably results in some muscle necrosis Such considerations and the promise of significant success in preserving ischemic myocardium probably have channeled efforts toward the pharmacologic manipulation of ischemic myocardium

However there appears to be sufficient information available to build a case that the immediate cause of infarction is coronary artery vasospasm [4] Excluding mechanical events as thrombosis what else but spasm can initiate a sudden episode of ischemia? The very absence of a demonstrable anatomic cause for the dramatic onset of ischemia in infarction suggests an abnormal physiologic state, as spasm Spasm has been indicted in variant or pre infarction angina [5] yet its crescendic [12] culmination e g infarction only rarely [3] is considered to have a spastic origin Also as vascular tone is related to the psyche spasm can explain how psychological factors can be translated directly to chest pain

It seems that the evidence for spasm far outweighs the interest it evokes and part of this neglect can be explained on historic grounds Spasm in one form or another has been considered in ischemic heart disease—angina pecto

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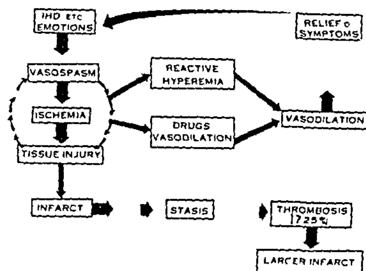


Fig 1 The injury vasospasm hypothesis considers coronary arterial spasm to be secondary to myocardial injury It is generally recognized that injury to vessels causes spasm as after needle puncture chemical irritation physical trauma or ischemia Stenotic atherosclerosis causes chronic ischemic myocardial injury which in conjunction with emotional factors initiates myocardial injury vasospasm Variant angina represents spontaneously reversed spasm and spasm might be reversed by appropriate vasodilators If spasm persists necrosis results causing a vicious cycle and acute infarction The fresh tissue injury perpetuates the spasm which causes continuing ischemia during the acute phase of the infarction Coronary artery stasis secondary to spasm may result in a secondary thrombus and by totally obstructing the blood supply causes infarction enlargement and sometimes cardiogenic shock

ns—for 200 years without proof of its existence and the biblical quotation[11] *Mene mene tel el u pharsin* (you have been weighed in the balance and found wanting) may be applicable A major objection to spasm has been that sclerotic arteries cannot contract, and the recent assertion that nitroglycerin has a peripheral action[1] has been a negative factor While not verbalized it probably has been assumed that coronary artery spasm is a short lived event as the spasm of variant angina and the cerebral spasm of migraine headaches[11] Therefore spasm cannot be a candidate for causing infarction, as the ischemia which initiates muscle necrosis is not an evanescent event but continues on into the acute phase of the infarction

Several years ago I found apparent vasospasm in experimental myocardial infarction[1] from which a hypothesis was developed which involves spasm in this disorder (Fig 1) This injury vasospasm hypothesis provides an explanation for major events in infarction and might obviate some of the objections to spasm For example the hypothesis considers spasm to be primarily intramyocardial (although it probably extends to the main artery), permitting spasm to occur in spite of calcified coronary arteries Instead of the usual adversary position between spasm and coronary artery atherosclerosis the hypothesis reconciles them and presents spasm as an injury reaction to the chronic ischemia of atherosclerosis Also the hypothesis holds that the spasm which initiates infarctions also continues during the acute phase of the infarction, and such spasm was observed experimentally[14] Recognition that there might be spasm during the acute course of clinical infarction should strengthen the case for spasm considering that the preservation of ischemic myocardium school is based on the appreciation of continuing ischemia during acute infarction

If, indeed infarctions are due to spasm there are a number of avenues to consider Antispasmodic therapy if administered early might abort the infarction and this would be more advantageous than acceptance of limitation of infarction size The reversal of spasm by antispasmodic agents prior to the onset of necrosis can be compared to variant angina where ablation of spasm is considered to occur spontaneously After infarction has supervened, vasodilative therapy should be more effective in dealing with the ischemia of acute infarction than non specific attempts to improve the myocardial oxygen supply demand ratio

The injury vasospasm hypothesis might provide some insight into cardiogenic shock, which has a mortality of over 85 per cent in most institutions[1] Patients who die from cardiogenic shock have large infarctions[1] and there is evidence that the extensive loss of myocardium occurred in a stepwise pattern with fresh necrosis occurring in close proximity to the onset of shock[1] Attempts to counter this devastating infarction enlargement have been by techniques to preserve ischemic myocardium The vasospasm hypothesis considers infarction enlargement leading to cardiogenic shock to be due, in most cases to secondary thrombosis Although it has been known that thrombi are more frequent in cases with cardiogenic shock than in those without this complication—71 per cent vs 15 per cent[17]—thrombi had not been implicated as the cause of the shock With spasm there is some flow into the ischemic area[18] and with complete loss of flow subsequent to a complicating thrombus the

infarction would enlarge Such thrombus induced infarction enlargement has been noted experimentally[1] In the few cases of cardiogenic shock without thrombi infarction enlargement probably is due to extension or increased severity of the original vasospasm

Also if infarctions are due to spasm it may be possible to progress beyond effective treatment of the acute attack to the prevention of infarctions This might be possible in spite of the presence of the underlying cause of infarctions i e coronary artery atherosclerosis Speculations might include ways to prevent or short circuit the psychic causes of vasospasm Chronic vasodilator therapy may be inappropriate as a prophylaxis considering that angina infarction and sudden death have followed withdrawal from chronic exposure to nitroglycerin in ammunition plants [?] Such cases also provide additional evidence that vasospasm can induce myocardial infarction

Fortuitously it appears that therapeutic programs designed by the preservation of the ischemic myocardium school can be used to gain information about the role of vasospasm in infarction Drugs[?] have been used successfully in those programs which according to the vasospasm hypothesis are operative against coronary artery spasm Intravenous nitroglycerin and sodium nitroprusside have been employed assuming they cause peripheral vasodilation which would then reduce end diastolic pressure and cardiac overload and thus help preserve ischemic myocardium The injury vasospasm hypothesis considers the primary beneficial effects of these vasodilators to be reduction of myocardial spasm and ischemia That nitroglycerin can reverse coronary artery spasm was recently demonstrated at surgery by direct observation The improved cardiac action after vasodilative treatment suggests that ischemic and noncontractile myocardium became functional The lessened chest pain arrhythmias and ischemia appear to speak for themselves A primary cardiac action for vasodilator treatment does not preclude the occurrence of helpful peripheral effects

Probably only minor modification of intravenous vasodilator therapy designed to reduce end diastolic pressure is needed to provide evidence about vasospasm According to the injury vasospasm hypothesis therapy might (1) abort infarctions (2) prevent cardiogenic shock and (3) improve myocardial function by reducing ischemia Evidence for the first two beneficial effects of vasodilators might be especially persuasive for vasospasm as the third improved myocardial function during infarction has already been demonstrated but is attributed to a peripheral effect Vasodilative therapy should be started as early as possible before necrosis supervenes and continued until the danger of cardiogenic shock is passed

The preservation of ischemic myocardium concept is growing in acceptance which is expected considering the wealth of propitious information which has been garnered However before treatment of infarction is completely harnessed to this philosophy it is hoped that alternative views such as vasospasm which do not have the inherent attitude that the acute event in infarction is irreversible and that some muscle necrosis is inevitable will be considered

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Clinical communications

Prognosis of right bundle branch block and left anterior hemiblock after intracardiac repair of tetralogy of Fallot

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Right bundle branch block and left anterior hemiblock may be caused by intracardiac repair of tetralogy of Fallot This was first reported by Kulbertus in 1968 8 per cent of his patients developed the combined lesion postoperatively and he expressed concern about the possibility of late complete heart block and death in these patients In 1972 papers by Wolff and associates and by Moss and co workers drew attention to an alarming incidence of complete heart block of late onset and sudden death in these patients

This article reports on a series of patients who underwent intracardiac repair of tetralogy of Fallot 22 per cent of whom developed right bundle branch block and left anterior hemiblock postoperatively The purpose of the article is to document the benign prognosis in these patients postoperatively and in late follow up and to discuss these findings in relation to contrary reports in the literature

Methods

A review was made of clinical records and ECG s of all patients who underwent open intracardiac repair of tetralogy of Fallot at the Montreal Children s Hospital from January 1968 to June 1972 Patients who died within 1 month of operation were considered to be operative deaths On the basis of the ECG on hospital discharge operative survivors were divided into four groups (1) no bundle branch block—QRS width 0 08 second or less (2) right bundle branch block—terminal slurred S wave in Lead I R in Lead V with QRS widening (incomplete 0 09 to 0 011 second complete 0 12 second or greater) (3) right bundle branch block and left anterior hemiblock—right bundle branch block plus Q waves of 0 02 second in Leads I and aV_L mean QRS axis of unblocked forces −30 to −120 degrees counterclockwise frontal plane vector loop (Figs 1 and 2) (4) complete heart block—idioventricular pacemaker with no conduction of supraventricular impulses rate under 50 per minute

The post hospital course and current status of patients were determined from review of clinic charts and ECG s and by letter and telephone contact with doctors of patients not followed in our clinic The information was augmented by telephone contact with the family or patient

Results

A total of 178 patients underwent open operation of these 25 died an operative mortality of 14 per cent (Table I) Of the 153 survivors the preoperative and postoperative ECG s were available for review on 141 (92 per cent) The 141 patients were distributed as outlined in Table II The focus of this report is on the 31 patients (22 per cent) who developed right bundle branch block and left anterior hemiblock postoperatively

Among these 31 patients only 2 developed a postoperative arrhythmia in each it was complete heart block while coming off cardiopul

From th Department f C diology Mont eal Children s Hosp tal, and McG ll Un rs ty Mo tre l Que Can da

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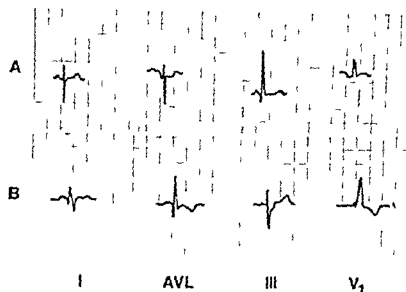


Fig 1 Selected ECG leads from Patient J P with tetralogy of Fallot A Preoperatively age 4½ months B Postoperatively age 4 years now showing right bundle branch block and left anterior hemiblock Note 0 02 second Q waves in Leads I and aV_L left axis deviation of unblocked forces and counterclockwise frontal plane vector loop

Table I Tetralogy of Fallot—intracardiac repair at Montreal Children s Hospital January 1958–June 1972

Total patients		178
Operative deaths	25 (14%)	
Survivors	153 (86%)	
Survivors		153
ECGs available	141 (92%)	

Table II ECG one month postoperatively—141 patients

No bundle branch block	27 (19%)
Right bundle branch block	82 (58%)
Right bundle branch block and left anterior hemiblock	31 (22%)
Complete heart block	1 (1)

Table III Right bundle branch block and left anterior hemiblock—31 patients

Postoperative arrhythmia	2
Complete heart block—6 days	
Complete heart block	
Nodal rhythm—7 days	
Late deaths	2
Right ventricular failure—4 months	
Repeat operation—20 months	
Survivors	29
Average survival 67 months	
Range (148–12)	
Late arrhythmias—0	

CHB = complete heart block

monary bypass In one a 13 year old girl normal sinus rhythm with right bundle branch block and left anterior hemiblock returned after 6 days In the other a 5 year old boy complete heart block was present intermittently for only a few hours to be replaced by a probable nodal rhythm which resolved after 7 days Both children had epicardial pacing wires and were paced as indicated until reliable normal sinus rhythm returned

Of the 31 patients with right bundle branch block and left anterior hemiblock postoperatively 29 are alive at present (Table III) an average of 67 months after operation (range 148 to 12 months) There have been no reports of arrhythmias and no ECG evidence of complete heart block All are doing well in terms of cardiac function as evidenced by physical examination and level of activities

Two patients have died late (Table III) The first of these was the 13 year old girl who developed transient complete heart block postoperatively in 1960 Although normal sinus rhythm returned digitalis was required for control of congestive heart failure Digitalis was stopped before discharge 2 months postoperatively but congestive heart failure returned after another 2 months She was rehospitalized and died 3 weeks later of progressive congestive heart failure There was no evidence of recurrence of complete heart block This death was considered to be related to an incomplete intracardiac repair The other patient was a boy age 4 years at his initial

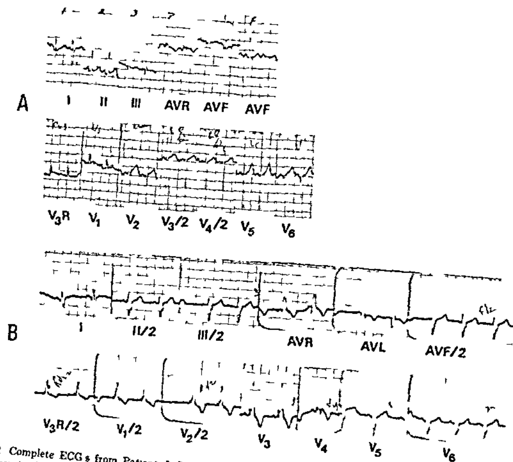


Fig 2 Complete ECG s from Patient J P with tetralogy of Fallot A Preoperatively age 4½ months B Postoperatively age 4 years

operation when severe infundibular stenosis was noted Twenty months later in 1966 reoperation was undertaken because of a persistent infundibular pressure gradient and a ventricular septal defect He died during this second open operation

Thus although two late deaths have occurred in this series of 31 patients neither could be attributed to the presence of right bundle branch block and left anterior hemiblock

Discussion

The combined lesion of right bundle branch block and left anterior hemiblock has been well described and widely reported in the adult cardiology literature In 1921 Wilson and Herrmann reported that the pattern now recognized as right bundle branch block and left anterior hemiblock could be produced by interruption of the right bundle branch and the anterior fascicle of the left bundle branch. Subsequent reports have developed the diagnostic criteria examined the pathologic basis discussed the etiologies and outlined the prognosis for this lesion Two recent reports have reviewed all of these aspects of the combined lesion

There has been controversy over the exact diagnostic criteria for right bundle branch block and left anterior hemiblock Criteria have applied to the initial 0 02 second vector the mean QRS axis the axis of unblocked forces and the inscription of the frontal plane vector loop The criteria chosen in the present study are adapted from those of Rosenbaum and are consistent with those of many other reports in the literature

In general there has been good correlation between the ECG evidence for right bundle branch block and left anterior hemiblock and the experimental interruption of the right bundle branch and left anterior fascicle in dogs and in primates Postmortem human studies have revealed appropriately located lesions to explain antemortem right bundle branch block and left anterior hemiblock

Table IV Prognosis of RBBB and LAH

Author	RBBB and LAH	Transient postop erative CHB		Late CHB or SD	
		Total	Followed by late CHB or SD	Total	Preceded by transient postoperative CHB
Cairns et al	31	2	0	0	0
Downing et al	14	2	0	0	0
Wolff et al	24	9	6 (67%)	3 CHB, 6 SD	6 (67%)
Moss et al	3	3	3 (100%)	3 CHB	3 (100%)
				12	9 (75%)

CHB = complete heart block LAH = left anterior hemiblock RBBB = right bundle branch block SD = sudden death

There are a number of etiologies of right bundle branch block and left anterior hemiblock in adults The reported frequency of each etiology varies widely among several large series in the literature Some authors have reported a high incidence of atherosclerotic coronary artery disease postulating chronic ischemia and fibrosis of the conducting system [7, 11, 1, 18, 19] Others have found coronary artery disease is less common in these patients and attribute the block to a primary sclero degenerative disease of the bundle branches and Purkinje network[9, 20] or to sclerosis of the left side of the cardiac skeleton [7, 1] Still others have considered the etiological roles of hypertension,[11, 1] aortic valve disease[6] previous myocarditis[7, 20] and cardiomyopathy [17]

The prognosis of these patients has not yet been fully delineated However when combined right bundle branch block and left anterior hemi block develops outside the setting of acute myocardial infarction, the prognosis is reasonably good The incidence of complete heart block has been reported at 10 per cent during an unspecified period of follow up by Lasser and associates [11] 6 per cent by Rosenbaum and associates,[7] and 13 6 per cent during an average 18 9 month follow up by Scanlon and associates [12] The life expectancy for this group may be no different from that of other patients in this age group who require an electrocardiogram [4]

The surgical creation of right bundle branch block was first reported by Kittle and co workers[23] in 1956, after repair of pulmonic stenosis whereas left anterior hemiblock (then described as left ventricular parietal block) was first reported by Samson and Bruce[24] in 1962, after transventricular aortic commissurotomy The combined lesion of right bundle branch block and left anterior hemiblock (then described as left superior intraventricular block) was first documented by Kulbertus[1] in 1968, after repair of ventricular septal defect and tetralogy of Fallot Several authors have since drawn attention to the occurrence of the combined lesion after intracardiac repair of tetralogy of Fallot [12, 25, 26, 2] Lev [5] and Rosenbaum and associates [6] have described the conduction system and its relation to the ventricular septal defect in tetralogy of Fallot The left posterior fascicle separates from the A V bundle at the posterior angle of the defect relatively well removed from the vicinity of the repair The left anterior fascicle and right bundle branch continue along the inferior margin of the defect and are at risk of damage from edema inflammation, hemorrhage, or suture The combined lesion of right bundle branch block and left anterior hemiblock develops with a reported incidence that varies from 7 per cent[27] to 10 7 per cent,[15] and 22 per cent in the present series

There are only three previously published series which report late follow up of right bundle branch block and left anterior hemiblock after open operation for tetralogy of Fallot In two of these[1, 4] there was a high incidence of complete heart block and sudden death In the third,[3] as in the present series neither occurred We have analyzed these reports in an attempt to explain these differences In the adult, complete heart block occurs when the progressive disease which involves the right bundle branch and left anterior fascicle extends into the distal His bundle or left posterior fascicle In the child undergoing intra cardiac repair of tetralogy, the right bundle branch and left anterior fascicle are at risk of damage, and right bundle branch block and left anterior hemiblock may appear However, once healing of the operative wound has occurred and there has been no evidence of trifascicular damage one might reasonably expect no progression of the conduction disorder—since no progressive disease is present We considered whether some of these patients might have trifascicular

disease in the postoperative period and whether these were the patients at high risk for late complete heart block and sudden death

The four series are analyzed in Table IV In the present series and in that of Downing and associates[29] transient postoperative complete heart block developed in only 2 of 31 and 2 of 14 patients respectively There were no episodes of late complete heart block or sudden death In Wolff and associates series' of 24 patients transient postoperative complete heart block occurred in 9 6 of whom went on to develop late complete heart block or to die suddenly A total of 9 patients developed late complete heart block or died suddenly 6 had had transient complete heart block postoperatively and 3 had had no previous arrhythmias Moss and associates in their series had 10 patients with tetralogy of Fallot in whom complete heart block of late onset developed Of these 10 only 3 had had right bundle branch block and left anterior hemiblock and all 3 had had transient postoperative complete heart block. Thus of 12 reported cases of complete heart block of late onset or sudden death in patients with right bundle branch block and left anterior hemiblock in 9 (75 per cent) transient complete heart block was noted in the postoperative period.

The process by which complete heart block resolves only to recur at some later date can only be postulated However it is reasonable to suppose that once the left posterior fascicle is damaged and complete heart block occurs even though resolution of acute inflammation and edema allows conduction to resume through this fascicle an ongoing process of fibrosis may be initiated which will eventually lead to permanent complete heart block The electrophysiologic correlate of such a sequence would be prolongation of the HV interval during normal sinus rhythm and block distal to the His deflection after development of late complete heart block

Clearly those children with transient postoperative complete heart block and residual right bundle branch block and left anterior hemiblock require close clinical and ECG follow up Consideration should be given to studies of the bundle of His in order to delineate the conduction status of the left posterior fascicle The documentation of HV conduction delay would suggest a high risk for the development of late onset complete heart block However the magnitude of this risk and consequently the role for prophylactic pacing in such children remain to be more clearly defined

The present series and that of Downing and associates indicate that the occurrence of right bundle branch block and left anterior hemiblock after intracardiac repair of tetralogy of Fallot does not of itself carry a high risk of late complete heart block or sudden death Our conclusion from the series of Wolff and of Moss and co workers is that the critical factor in a bad late prognosis in patients with postoperative ECG evidence of right bundle branch block and left anterior hemiblock may be the history of transient postoperative complete heart block—indicative of trifascicular disease in this setting

Summary

One hundred and forty one survivors of intracardiac repair of tetralogy of Fallot (TOF) operated on between 19ɔ8 and 1972 were studied in order to document the incidence of right bundle branch block and left anterior hemiblock (RBBB and LAH) and to define the late prognosis RBBB and LAH occurred in 31 patients (22 per cent) all of whom have had complete follow up Transient complete heart block (CHB) occurred postoperatively in 2 patients there were no other significant arrhythmias Two late deaths have occurred neither from arrhythmia (one from progressive congestive heart failure and the other from attempted reclosure of a ventricular septal defect) The remainder of the patients are well an average of 76 months postoperatively (range 144 to 12 months)

The absence of late onset CHB or sudden death in this series contrasts with the relatively high incidence of these events in some studies of RBBB and LAH after intracardiac repair of TOF However in those reports a history of transient postoperative CHB (indicative of trifascicular disease in this setting) can be found in 75 per cent of those who developed late onset CHB or died suddenly We conclude that the occurrence of RBBB and LAH after intracardiac repair of TOF does not of itself carry a bad late prognosis The critical factor in a bad late prognosis in patients with ECG evidence of RBBB and LAH may be the history of transient postoperative CHB

Addendum

Since the preparation of this report and its presentation in abstract form Godman and asso

ciates have published similar conclusions (Circulation 49 214 221 1974) They studied 14 patients with postoperative right bundle branch block and left anterior hemiblock Four of those patients developed late onset complete heart block, all 4 of them having had transient postoperative complete heart block Studies of the bundle of His placed the block distal to the bundle of His in all 4 Six additional patients of the group had had transient postoperative complete heart block and in 5 of the 6 the HV time was prolonged Transient postoperative complete heart block was judged to identify a group of patients with postoperative right bundle branch block and left anterior hemiblock at particularly high risk of developing late onset complete heart block

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Angina pectoris with normal coronary arteriograms Hemodynamic and metabolic response to atrial pacing

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In 1910 Osler described a young man who suffered for several years with recurrent angina pectoris After his death postmortem examination revealed normal coronary arteries Since then there have been a number of reports of patients presenting with chest pain suggestive of myocardial ischemia in whom coronary arteriograms have been normal The etiology of this syndrome has not been clarified but several explanations have been suggested including inadequate coronary arteriography abnormalities of mall coronary vessels abnormal hemoglobin oxygen dissociation and hyperdynamic left ventricular contraction resulting in increased myocardial oxygen consumption In this group abnormalities of myocardial lactate metabolism indicating anaerobic glycolysis have been shown during isoproterenol infusion and atrial pacing Abnormal left ventricular function has been demonstrated during exercise These previous studies have included patients with clinical evidence of myocardial disease conduction disturbances in the resting electrocardiogram (ECG) and a large number with negative postexercise ECGs The present study was the first undertaken to assess the hemodynamic and metabolic changes during pacing induced tachycardia in a group of patients with chest pain no clinical evidence of myocardial disease positive double Masters two step tests and normal coronary arteriograms.

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Materials and methods

Sixteen women and one man ranging in age from 36 to 58 years with chest pain suggestive of myocardial ischemia were studied Routine assessment included the history and physical examination blood count, urinalysis fasting blood sugar serum cholesterol total serum lipids or serum triglycerides and posteroanterior and lateral x ray views of the chest A 12 lead ECG was recorded at rest and following a double Masters two step test tracings being obtained immediately and at 2 minute intervals for 10 minutes after exercise

The patients were given 100 mg of sodium pentobarbital orally one hour before the procedure and were studied in the fasting state Under local anesthesia the brachial artery and two veins were isolated in the right antecubital fossa A No 8 Sones catheter was introduced into the left ventricle from the brachial artery A No 7 or 8 single lumen Cournand catheter was placed so the tip lay in the main pulmonary artery Pacing was achieved by a No 8 Gorlin catheter placed in the mid portion of the coronary sinus The left brachial artery was cannulated with a short Teflon catheter by the Seldinger technique

Lead II of the ECG and pressures from the pulmonary artery brachial artery and left ventricle were recorded during a 10 minute control period The cardiac output was measured in duplicate by the dye dilution technique during the final 2 minutes of the control period and simultaneous blood samples for lactate concentration were taken in duplicate from the coronary sinus and brachial artery Atrial pacing was then carried out at rates varying from 132 to 160 per minute (mean 143 per minute) Pacing was interrupted for 15 second periods after 1 3 and 4¼ minutes Cardiac output was determined between

5 and 7 minutes and duplicate blood samples for determination of plasma lactate concentration were obtained between 8 and 10 minutes and then pacing was discontinued

Pressures were obtained with P23 Db Statham strain gauges from a zero reference level of 5 cm below the angle of Louis Recording speed was normally 25 mm per second, but a speed of 100 mm per second at high sensitivity was used to record left ventricular end diastolic pressure (LVEDP) Left ventricular stroke work index (LVSWI) in gram meters per square meter was calculated using the formula

$$LVSWI = \frac{SI \times (BAm - LVEDP) \times 13.6}{1000}$$

SI = stroke index in milliliters per square meter and BAm = brachial artery mean pressure in millimeters of mercury Blood was analyzed for lactate concentration as in a previous report [12]

Following completion of the studies, selective cinecoronary angiography with the Sones technique and left ventriculography was carried out in all patients and recorded on 35 mm film The left ventriculograms obtained in the right anterior oblique position were analyzed with the one plane cineangiographic measurement of left ventricular volume Tracings of end systolic and end diastolic volumes were made from the cine angiograms The ejection fraction (EF) was computed from the ratio of stroke volume to end diastolic volume

Results

Clinical The historical data in each patient were critically reviewed All were considered to have angina pectoris according to the criteria as outlined by Hurst and Logue [13] None had previous evidence of myocardial infarction In two patients there was a history of hypertension treated for a short time with hydrochlorothiazide In each case this had been discontinued for at least one year prior to investigation Six patients smoked 20 or more cigarettes per day Four had undergone cholecystectomy One patient had a hiatus hernia the symptoms of which were easily differentiated from her anginal pain A family history of diabetes mellitus was present in one hypertension in two and myocardial infarction in six In four of these the infarction occurred before the age of 50 Arterial blood pressure was normal in all patients (<140/90) and the clinical examination of the heart was within normal limits The chest x rays were normal in all subjects

Laboratory Hypercholesterolemia (>250 mg per 100 ml) was found in seven patients. Triglyceride levels were determined in eight and found abnormal (>150 mg per 100 ml) in three including one with elevated serum cholesterol In the six patients where total lipids were determined rather than triglycerides values greater than 1,000 mg per 100 ml were found in two one of whom also showed hypercholesterolemia In all patients the fasting blood sugar was 100 gm per 100 ml or less and none was anemic

Electrocardiogram Six patients had a normal ECG at rest and 11 were abnormal, showing non specific ST T abnormalities All patients had an abnormal postexercise ECG using the double Master's two step test and the Mattingly criteria of greater than 0 5 mm flat ST segment depression in one or more leads

Angiography Left ventricular cineangiography showed normal chamber size Thirteen of 17 left ventriculograms were suitable for determination of the EF The mean EF was 70 ± 9 per cent (S D) (range 50 to 82 per cent) Two patients had minor degrees of prolapse of the posteromedial scallop of the posterior mitral valve leaflet Neither of them had mitral regurgitation Selective coronary arteriography was done in multiple projections and angiograms of high quality were obtained These were considered to be normal by two or more observers

Response to atrial pacing Thirteen patients developed chest pain during pacing, two had worsening of chest pain that was present during the control period and two were symptom free The hemodynamic and metabolic data during sinus rhythm and pacing induced tachycardia are summarized in Table I

The technical difficulty in determining the isoelectric point on the PR segment during pacing negated accurate assessment of the degree of ST segment depression Therefore ST segment depression was taken to be significant if it occurred during interruption of pacing or during the immediate postpacing period Thirteen patients had isoelectric ST segments during the control period and five of these showed straight ST segment depression of 0 5 mm or more during interruption of pacing and in the postpacing period Three patients with ST segment depression in the

control period showed further depression of 0 5 mm or more

The heart rate (HR) during the control period was 85 ± 11 beats per minute (range 64 to 108) during pacing it was 143 ± 8 beats per minute (range 132 to 160) Immediately after pacing the rate was 85 ± 11 beats per minute (range 60 to 100)

LVEDP averaged 8 ± 2 mm Hg during sinus rhythm (range 5 to 13) and fell during pacing to 4 ± 3 mm Hg returning to normal values during interruption and in the postpacing period In one patient LVEDP was 13 mm Hg during the control period and did not change during pacing

The cardiac index (CI) was 3 5 ± 0 5 L per minute per square meter during the control period and it did not change significantly during atrial pacing The mean systemic pressure during sinus rhythm was 96 ± 8 mm Hg and it did not change with tachycardia The SI fell from 40 ± 8 to 25 ± 5 ml ($P < 0\,001$) and the stroke work index decreased from 48 ± 8 to 30 ± 5 Gm M per square meter during pacing ($P < 0\,001$)

Data relating to myocardial lactate metabolism are available in 15 of the 17 patients during the control period and in 16 during atrial pacing In the control period 13 patients showed a normal pattern of myocardial lactate metabolism with extraction of 10 per cent or greater One patient showed lactate extraction of 3 per cent and the other showed lactate production of 12 per cent in the absence of chest pain In the 13 patients with normal lactate metabolism during the control period two became abnormal during pacing in association with chest pain One showed lactate extraction falling from a control level of 25 to 8 per cent and the other changed from lactate extraction of 11 per cent to lactate production of 26 per cent The two patients with abnormal lactate metabolism during the control period experienced pain with pacing One continued to show lactate extraction of 3 per cent and the other increased lactate production from 12 to 26 per cent

Discussion

Seventeen patients have been described who presented with chest pain and abnormal postexercise ECG in whom coronary arteriography showed no occlusive coronary artery disease There has been considerable controversy over the specificity and sensitivity of the double Master s two-step test and Fitzgibbon and co workers recently reported a 16 per cent incidence of false positive tests in a group of 160 men with suspected coronary artery disease Recently Cumming Dufresne and Samm[13] have reported that the incidence of an ischemic ECG pattern during or after exercise ranged from 20 to 50 per cent in women between 40 and 60 years of age without a history of cardiovascular disease The patients in this present group represent part of a false-positive population but they do permit an opportunity to examine metabolic and hemodynamic events in patients who clinically were considered to have coronary artery disease

Until recently little was known about the hemodynamic or metabolic events associated with angina pectoris due to coronary artery disease Investigations have however, been carried out during angina occurring spontaneously or provoked by drugs exercise and most recently by atrial pacing[1, 16, 20] Several reports have demonstrated the value of atrial pacing in the study of left ventricular function and myocardial metabolism in patients with coronary artery disease When angina is induced by tachycardia there is a good correlation between the development of chest pain ST segment depression myocardial lactate production and abnormal left ventricular function[16] In contrast to this of the 15 patients in the present series who had chest pain during pacing only seven showed ST segment depression four demonstrated abnormal myocardial lactate metabolism and only one showed abnormal left ventricular hemodynamics In this case left ventricular stroke work fell during pacing but there was not an appropriate decrease in left ventricular filling pressures as would be expected by the Starling relationship The remaining 14 patients with pain and the two patients without discomfort during pacing showed a reduction in left ventricular filling pressure during tachycardia in association with a decrease in stroke work and thus had normal pacing ventricular function curves

The hemodynamic response to exercise in a group of 10 patients with chest pain and normal coronary arteriograms has been reported[10] Four of these patients developed chest pain during exercise and in each there was a marked increase in LVEDP The response was almost identical to that seen in another group of patients with

5 and 7 minutes and duplicate blood samples for determination of plasma lactate concentration were obtained between 8 and 10 minutes and then pacing was discontinued

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Table I Cont d

Patient	HR (beats/min)	CI (L/min/M)	SI (ml/M)	BAm (mm Hg)	LVEDP (mm Hg)	LVSWI (Gm M/M)	ST (mm)	EF (%)	Lactates A (mg/100 ml)	Lactates CS (mg/100 ml)	Lactates Uptake (%)	Chest pain
P G												
Control	108	3 [illegible]	35	100	8	44	0		11 0	10 3	+11 2	No
Pacing	150	3 3	[illegible]	87	0	[illegible]	−0 5		10 5	13 [illegible]	−2[illegible]	Yes
Interrupt	90				8		0					
F M												
Control	[illegible]	3 4	34	100	5	44	0	[illegible]	6 9	4 8	+30 4	No
Pacing	155	3 4	[illegible]	112	3	3[illegible]	−0 [illegible]		6 9	4 4	+36 2	Yes
Interrupt	93				5		−0 [illegible]					
B S												
Control	9[illegible]	0	2[illegible]	98	[illegible]	3	0	6[illegible]	[illegible]2	4 0	+23 [illegible]	No
Pacing	140	2 0	14	10	4	19	0					Yes
Interrupt	98				7		0					
E F												
Control	90	8	33	9[illegible]	6	39	0	60	5 4	4 8	+11 1	No
Pacing	13		0	9[illegible]		24	−3 0		5 6	5 0	+10 7	No
Interrupt	84				10		−1 [illegible]					
F R												
Control	84	3 4	38	100	10	46	0	[illegible]9	[illegible]3	5 8	+20 [illegible]	Yes
Pacing	150	3 4	[illegible]	108	6	30	−[illegible]0		[illegible]	6 2	+13 9	Yes
Interrupt	84				10		−1 5					
L H												
Control	9[illegible]	3 3	34	109	6	48	−1 0	[illegible]	11 3	9 0	+20 4	Yes
Pacing	160	3[illegible]	[illegible]	11[illegible]	[illegible]	34	−4 0		[illegible]8	2	+ 7	Yes
Interrupt	100				[illegible]		−[illegible]0					
L B												
Control	[illegible]	3 6	40	10[illegible]	8	5	−1 0		11 4	1[illegible]8	−12 3	No
Pacing	14	3 8	[illegible]6	100	4	34	−4 0		11 9	15 0	−[illegible]6 1	Yes
Interrupt	94				10		−[illegible]0					
C M												
Control	1	6	36	100	[illegible]	44	0	50	11 3	9 0	+[illegible]0 4	No
Pacing	130	3 0	1	10[illegible]	11	29	0		11 0	10 3	+11 2	Yes
Interrupt	[illegible]				1[illegible]		0					
Summary 11 patients (Mean ± S D)												
Control	8[illegible] ± 11	3 [illegible] ± 0 5	40 ± 8	9[illegible] ± 8	8 ± [illegible]	48 ± 8	0	0 ± 9	[illegible] ± 2 4	6 4 ±	19 5 ± 14 8	
Pacing	143 ± 8	3 [illegible] ± 0 7	2[illegible] ± 5	9 ± 10	4 ± 3	30 ± 5	−1 3		7 4 ± [illegible]3	6 6 ± 3 4	15 2 ± [illegible]1 6	
Interrupt	8 ± 11				9 ± 3		−0					

normal response seen in all but one of our patients during atrial pacing In the presence of occlusive coronary artery disease however angina induced by atrial pacing is usually associated with abnormalities of LVEDP particularly a rise in pressure during interruption of pacing This pattern was not seen in the present group of patients who showed responses similar to normal subjects and patients with coronary artery disease who do not develop ischemia during pacing

Arbogast and Bourassa showed normal pacing ventricular function curves obtained by plotting LVSWI against LVEDP in their group of 10 patients with angina and normal coronary arteries They showed an elevated CI during pacing This finding has not been our experience in this group and in previous reports in normal subjects and patients with coronary artery disease The objective criterion used by Arbogast and Bourassa to include patients into the study was ST segment changes present during atrial pacing Interpretation of ST segment depression during atrial pacing is difficult Artifactual ST segment depression may result from the prolonged PR interval which at rapid rates may superimpose

Table I Hemodynamic and metabolic data in patients with angina and normal coronary arteries

Patient	HR (beats/min)	CI (l/min/M²)	SI (ml/M²)	BAm (mm Hg)	LVEDP (mm Hg)	LVSWI (Gm M/M²)	ST* (mm)	EF (%)	Lactates: A (mg/100 ml)	Lactates: CS (mg/100 ml)	Lactates: Uptake (%)	Chest pain
P D												
Control	64	3 2	49	107	13	62	0	68	11 5	7 8	+3?2	No
Pacing	135	4 7	3[illegible]	101	13	42	−2 0		11 3	6 9	+38 9	Yes
Interrupt	60				14		−1 0					
C D												
Control	88	3 7	43	101	10	51	0	76	4 8	4 0	+16 [illegible]	No
Pacing	141	3 3	23	103	3	31	0		4 8	4 0	+16 7	Yes
Interrupt	8[illegible]				10		0					
V H												
Control	8[illegible]	3 [illegible]	43	102	8	55	0	77	5 8	3 5	+39 7	No
Pacing	13[illegible]	3 [illegible]	28	100	2	3[illegible]	0		5 8	3 5	+39 7	Yes
Interrupt	86				9		0					
H M												
Control	74	3 9	51	84	8	[illegible]6	0		6 5	3 5	+46 2	No
Pacing	13[illegible]	3 9	29	86	3	33	0		6 4	3 2	+50 0	Yes
Interrupt	76				10		0					
A B												
Control	77	4 3	5[illegible]	89	12	58	0		7 5	6 5	+13 3	
Pacing	150	[illegible] 1	31	98	8	42	−2 0		7 5	6 5	+13 3	Yes
Interrupt	88				14		−1 0					
J S												
Control	80	4 0	50	90	10	54	0	76	6 8	5 6	+17 6	No
Pacing	140	4 0	29	9[illegible]	[illegible]	2[illegible]	0		8 1	7 0	+13 6	Yes
Interrupt	82				9		0					
B S												
Control	69	2 [illegible]	40	89	10	43	0	79				No
Pacing	13[illegible]	3 2	21	89	3	28	0					No
Interrupt	67				10		0					
E C												
Control	98	3 [illegible]	3[illegible]	87	10	37	0	82	6 1	4 7	+[illegible]3 0	No
Pacing	150	3 8	26	81	[illegible]	28	0		6 4	5 6	+12 5	Yes
Interrupt	90				10		0					
F H												
Control	8[illegible]	2 8	33	88	5	37	−1 0	76	6 0	5 8	+3 3	No
Pacing	1[illegible]0	2 7	18	83	2	18	−2 5		6 9	6 7	+2 8	Yes
Interrupt	84				8		−1 5					

Abbreviations ST = electrocardiographic ST segment change A = arterial CS = coronary sinus Uptake = $\frac{A-CS}{A} \times 100$

angina pectoris and documented coronary artery disease It should be noted however, that of the 10 patients with angina pectoris and normal coronary arteriograms only three had abnormalities in the postexercise ECG Seven patients showed elevated resting LVEDP two had cardiomegaly and one had left bundle branch block thus this group is quite different from our population

Bemiller Pepine and Roger[11] have recently studied a group of patients with angina pectoris and normal coronary arteriograms Their patients had either an abnormal postexercise ECG or abnormal myocardial lactate metabolism during pacing In a subsequent exercise study there was an increase in LVEDP from 11 to 19 mm Hg but these changes were much less than those seen in patients with angina and coronary artery disease during supine leg exercise Previous investigations in our laboratory would suggest that exercise is a superior stress to pacing for the assessment of hemodynamic abnormalities in patients with coronary artery disease[19] This factor could explain the discrepancy in the abnormal left ventricular function reported by Dwyer and co workers[10] during exercise and the

cardial lactate metabolism in 70 per cent of the patients In the present study left ventricular function was normal in 16 of 17 patients and four of 16 showed abnormal myocardial lactate metabolism The normal left ventricular function and increased left ventricular contractility seen are incompatible with true myocardial ischemia However as noted by Kemp[28] the extent or distribution of ischemia in these patients may be such as to account for the lack of hemodynamic change

Summary

Seventeen subjects ranging from 36 to 58 years of age presented with chest pain suggestive of myocardial ischemia Each patient had a positive double Master s two step test with ST segment depression of 0 5 mm or more in the postexercise ECG In each case coronary angiography and left ventriculography were normal Hemodynamic and metabolic investigations were carried out during sinus rhythm and atrial pacing Thirteen patients experienced pain during pacing but only one showed an abnormal hemodynamic response Two patients showed abnormal myocardial lactate metabolism during the control period and four during pacing induced tachycardia The increase in ejection fractions in this group suggests hyperdynamic ventricular contraction which could result in increased oxygen requirements and thus induce ischemic pain in the absence of arteriographically demonstrable coronary artery disease

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the pacing artifact and P wave with either the QRS complex or the ST segment

Myocardial lactate metabolism in patients with angina and normal coronary arteriograms is of particular interest Animal studies have shown that absolute lactate production by the heart occurs only in situations of marked hypoxia such as a reduction of arterial flow to the left ventricle to 25 per cent of control values [22] In 17 patients with coronary artery disease who developed angina during atrial pacing, 13 showed lactate production and all had ST segment depression [16] Kemp, Elliott and Gorlin[2] reported 50 patients with the anginal syndrome and normal coronary arteriograms Eleven of 14 patients showed abnormal myocardial lactate metabolism with isoproterenol stress Neill, Kassebaum, and Judkins[9] reported a similar case during atrial pacing In an expanded series of 11 patients, however, these investigators have shown normal lactate metabolism in the additional 10 [3] Arbogast and Bourassa [1] showed lactate production of five of 10 patients with this syndrome

In the series of Kemp and co workers[7] the resting ECG was abnormal in seven of 11 patients who showed abnormal lactate metabolism The patient described by Neill Kassebaum, and Judkins[9] who demonstrated lactate production during pacing also had an abnormal resting ECG All four of our patients with abnormal myocardial lactate metabolism during pacing had abnormal ECG s at rest and developed pain during pacing

The mechanism of angina in the presence of normal coronary arteriograms is still uncertain Eliot and Bratt[4] have found abnormal hemoglobin oxygen dissociation in 14 of 15 patients with the anginal syndrome and normal coronary arteriograms All had ECG evidence of ischemia as evidenced by a positive Master s test or both ECG and enzymatic evidence of myocardial necrosis Eight were heavy smokers and reversal of abnormal hemoglobin oxygen dissociation was observed in three after smoking was discontinued Carboxyhemoglobin levels have been studied in patients with coronary artery disease who smoke [23] Myocardial anaerobic metabolism was demonstrated in these patients at levels of carboxyhemoglobin between 5 and 10 per cent The four patients in our series showed abnormal myocardial lactate metabolism were nonsmokers

Occlusive disease of the small coronary arteries has been suggested as an alternate etiologic consideration, although autopsy reports have not substantiated this [4] In a report of 112 myocardial biopsies by Shirey[24] there was evidence of non atherosclerotic small vessel disease in only two patients There was no atherosclerotic small vessel disease Regional myocardial blood flow studies were reported in seven patients with angina and normal coronary arteriograms and compared with 10 normal subjects [5] Myocardial blood flows in three areas of the left ventricle were similar to those in normal subjects Likewise, the mean myocardial blood flows from the entire left ventricle right ventricle, and right atrium were normal The data suggested that small vessel disease or nonvisualized atheroma is not the basis for angina in these patients James [6] has stated that it is improbable that the majority of patients with angina and allegedly normal coronary arteriograms have abnormal small coronary arteries

Technically poor coronary angiograms and underestimation of the pathology during interpretation of the coronary angiogram must always be considered In our opinion this is unlikely since angiograms of high quality were obtained in several projections and widely patent coronary arteries were seen

Hyperdynamic left ventricular contraction inducing a state of increased myocardial oxygen consumption has been proposed as a mechanism for the pain in this syndrome Pepine, Bemiller, and Schang [7] have shown a rise in left ventricular oxygen consumption during tachycardia utilizing the coronary sinus thermodilution technique Sample and co workers[?] and Boden and associates[?] have reported increased EF as evidence of hyperdynamic left ventricular contractility Sample and co workers showed prolonged ejection time in their patients These results suggest increased oxygen demand and diminished supply because of prolonged ejection time may result in the production of pain In our group 10 of 13 patients had EF s greater than 65 per cent The beneficial effects of propranolol in this syndrome provide further support for the concept that increased left ventricular contractility may be involved in the production of pain in these patients

In previous reports from our laboratory,[12, 16] ischemic pain in patients with coronary artery disease was associated with abnormal left ventricular function in the majority and abnormal myo

Table I Number sex age range and median age of the patients in the three disease groups

Disease group	No of patients			Age range	Median age		
	Men	Women	Total		Men	Women	Total
Sudden death	33	14	47	44 90	62	72 5	64
Chronic coronary	17	4	21	46-83	69	74.5	71
Noncoronary	7	6	13	48 78	61	67.5	65

Then the main epicardial arteries were removed and prepared separately

Large myocardial blocks were obtained from standard sites in the ventricles and atria Tissue blocks containing the sinus and atrioventricular nodes were treated according to the methods of Hudson and James[5] respectively for demonstration of the conduction nodes The proximal 2 to 3 cm of the bundle branches were included in the interventricular septal blocks

The tissue was postfixed in Helly s solution for 24 hours and then rinsed in flowing tap water for another 24 hours After paraffin embedding one section was cut from each block The sections were stained with Lendrum s martius scarlet blue (MSB) method Other stains used for selected additional sections were Mallory s phosphotungstic acid hematoxylin and hematoxylin and eosin

The myocardial sampling has been described more extensively in a previous report

Microscopy The microscopical examination was carried out without knowledge of clinical or autopsy data The median number of tissue blocks examined from each heart was 33 Microscopic scanning of one section from each block was carried out at a magnification of 100× and the following lesions were recorded

Chronic inflammatory microlesions The lesions were of microscopical size usually 0 3 by 0 3 mm or less in the plane of section They consisted of mononuclear inflammatory cells accumulating between myocardial cells and connective tissue fibers The surrounding myocardium appeared normal Chronic inflammatory changes sometimes occurring in close contact with healing or old infarcts were not included

Lesions of the conduction system Fibrous lesions included general or focal increase of collagen fibers in the conduction tracts No attempt was made to decide whether the increase was real or only apparent due to loss of muscle cells Fibrosis of the sinus and atrioventricular nodes was graded subjectively from 1 to 4 *Grade 1* slender strands of collagen fibers intermingling with muscle cells *Grade 2* thick strands of collagen fibers intermingling with and apparently replacing some muscle cells *Grade 3* collagen fibers more predominant than in Grade 2 in some regions replacing up to 50 per cent of the muscle cells *Grade 4* coarse strands of collagen fibers in some regions replacing more than 50 per cent of the muscle cells

In order to test the reproducibility of the grading nodal tissue in 50 selected sections was graded twice during the study Agreement in the grading was seen in 44 of the 50 sections

The bundle of His was included in the grading Fibrosis of the bundle branches was noted but not graded

Nonfibrous lesions of the conducting system would include inflammatory neoplastic and myodegenerative changes as well as recent or healing infarction

Myocardial infarcts The age of the infarcts was roughly determined according to the morphologic criteria of Mallory White and Salcedo Salgar and Lodge Patch[8] The infarcts were *recent* (48 hours old or less) *healing* (48 hours to 3 to 4 weeks) or *old* (older than 3 to 4 weeks) Old infarcts had to be larger than 1 by 1 cm in the plane of section in order to be recorded whereas recent and healing infarcts of any size were noted

Statistical analysis For statistical analysis of the results the Wilcoxon rank sum test or the chi square test with Yates correction was applied Two tailed tests were used throughout P values of 5 per cent or less were considered to be statistically significant

Results

The age and sex of the patients are shown in Table I

Myocardial lesions in sudden, unexpected coronary death

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In previous reports acute lesions were described in the large and small coronary vessels in cases of both sudden coronary death and in control subjects[1] The acute lesions were ascribed a role in the pathogenesis of sudden coronary death Other factors however could also be of importance for the sudden coronary deaths e g, myocardial lesions which could render the myocardium especially vulnerable to disturbances of the coronary blood flow

The present study was carried out in order to examine whether the frequency of lesions of the myocardium and the conduction system differed between cases of sudden coronary death and controls

The following myocardial lesions were studied (1) small myocardial infiltrates of chronic inflammatory cells (2) fibrous and other lesions of the conduction system (3) myocardial infarcts of any age Further the heart weight was compared in cases of sudden coronary death and in the control subjects

If found a higher prevalence of myocardial lesions and larger heart weights among the sudden coronary death patients compared with the other patients would suggest a relation between such lesions and sudden coronary death

Material and methods

The patients were identical with those described in previous reports[1,3] They comprised 81 cases which were selected consecutively from an autopsy population Based on the clinical data the cases were divided into three groups

Sudden coronary death In this group were 47 patients with no recent clinical disease who had died instantly or within 10 minutes after the onset of chest pain

Chronic coronary disease This group comprised 21 patients who had been treated for myocardial infarction 6 months to several years previously Now all had died of major noncardiac diseases

Noncoronary disease The 13 patients in this group had died of major diseases without known cardiac disease

During the subsequent examination of the myocardium clinically silent, recent infarcts were detected in some of the control subjects (chronic coronary and noncoronary patients) These patients were not excluded for the following reason infarcts less than a few hours of age cannot be detected by the conventional histological methods applied in this study Therefore it was unlikely that *all* control patients with acute infarcts could be excluded on the basis of histological criteria alone Consequently, it was decided to maintain only clinical criteria for the selection of cases

More details from the selection of cases have been given elsewhere[1]

All deaths were witnessed

Autopsy procedure Complete autopsies were carried out 8 to 35 hours after death The hearts were removed by opening the pericardial sac and cutting the exposed large vessels close to the heart Clotted or liquefied blood in the atria and the ventricles was removed through the intact ostia before the heart weight was noted The unopened hearts were immersed in 20 per cent unbuffered formaldehyde solution for 6 weeks

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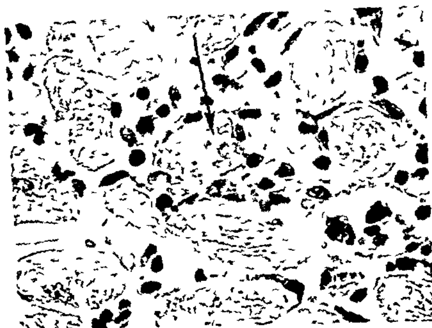


Fig 3 The same lesion as shown in Fig 2 at a larger magnification The injured muscle cell (arrow) is shrunken and apparently there is loss of myofibrils The *inflammatory* infiltrate *consists* of lymphocytes and a few large *mononuclear cells*. (Lendrum's MSB stain × 900)



Fig 4 Two or three muscle cells partly injured and infiltrated by mononuclear cells mainly lymphocytes. The adjoining parts of the affected muscle cells appear normal (Lendrum's MSB stain × 580)

2.5μ to about 2 500 by 2 500μ in the plane of section and the majority of lesions had a size of 100 to 300 by 100 to 300μ

Generally several microlesions were observed in various parts of each heart No predilection site for the microlesions appeared. Sometimes they occurred in the neighborhood of old or healing infarcts but their occurrence in these regions was not more frequent than in noninfarcted parts of the hearts

Chronic inflammatory microlesions were seen in some patients in each of the three disease groups The lesions were significantly more frequent among the sudden death patients



Fig 1 Small chronic inflammatory infiltrate consisting of lymphocytes and a few large mononuclear cells (*m*) The muscle cells and a capillary (*c*) appear normal (Lendrum's MSB stain × 580)



Fig 2 Small interstitial infiltrate of mononuclear inflammatory cells One single muscle cell appears to be injured (arrow) and the other muscle cells normal (Lendrum's MSB stain × 350)

Chronic inflammatory microlesions In chronic inflammatory microlesions, mainly lymphocytes but also small numbers of plasma cells, granulocytes, and histiocytes had accumulated between apparently normal muscle cells (Fig 1) Frequently, one or a couple of injured muscle cells were observed within the inflammatory lesion (Figs 2 and 3) Injured muscle cells could be invaded by mononuclear inflammatory cells even in the absence of a surrounding interstitial infiltrate (Fig 4) In such cases interstitial inflammatory infiltrates always were present in other regions of the hearts

The size of the microlesions ranged from 25 by

Table III Number and per cent of patients with fibrosis grades 1 to 4 of the sinus node*

Disease group†	No of patients				
	Total	With fibrosis grade			
		1	*2*	*3*	*4*
Sudden death	4	0	8 (1[illegible]%)	31 (66[illegible])	8 (1[illegible]%)
Chronic coronary	19	1 (5%)	4 ([illegible]1%)	13 (68[illegible])	1 (5[illegible])
Non-coronary	11	0	6 ([illegible])	5 (4[illegible]%)	0

*In Tables III and IV four and [illegible] cases, respectively, were excluded from the original material of 61 patients since all standard sections from the [illegible] nodes were not available
†Sudden death vs noncoronary χ^2 = 49[illegible]8 0 10 > P > 0 0[illegible]

Table IV Number and per cent of patients with fibrosis grades 1 to 4 of the atrioventricular node*

Disease group	No of patients				
	Total	With fibrosis grade			
		1	*2*	*3*	*4*
Sudden death	46	11 (24[illegible])	34 ([illegible]4%)	0	1 ([illegible]%)
Chronic coronary	19	3 (16[illegible])	10 (53[illegible])	4 ([illegible]1%)	[illegible] (11[illegible])
Noncoronary	11	1 (9[illegible])	10 (91[illegible])	0	0

*See footnote of Table III

Table V *Number and per cent of patients with myocardial infarcts*

Disease group	No of patients				
	Total	With infarct			*Without Infarct*
		Recent	*Healing*	*Old*	
Sudden death	4	6 (13[illegible])	6 (13%)	3[illegible] (9[illegible])	8 (1 %)
Chronic coronary	[illegible]	4 (19%)	4 (19[illegible])	20 (9[illegible])	1 (5[illegible])
Noncoronary	13	1 (8[illegible])	0	0	12 (92%)

myocardial vessels of several patients in the present series Therefore it is of particular interest that experimental platelet microembolization may cause myocardial lesions resembling those described in the present paper [7] Subclinical platelet microembolization may have caused some of the present chronic inflammatory microlesions The high frequency of microlesions among the sudden death patients could either be due to more microembolization in these patients compared with the chronic coronary and noncoronary patients or because the myocardium of the sudden death patients could be more vulnerable to microembolism

Lesions of the conduction system The frequency of graded fibrous lesions was similar in the sudden death and chronic coronary groups Nonfibrous lesions of the conduction system occurred in 10 of the 46 sudden death patients and in none of the chronic coronary or noncoronary patients In seven of the 10 sudden death patients the lesions were chronic inflammatory microlesions which occurred elsewhere in the hearts as well The actual significance of the lesions in individual cases cannot be determined One explanation could be that conduction disturbances or arrhythmias occur more readily among patients with morphological lesions in the conduction system compared with patients without such lesions

Myocardial infarcts Recent myocardial infarcts were found in small and similar propor

Table II Number and per cent of patients with chronic inflammatory microlesions in three disease groups

Disease group	No of patients	%
Sudden death	38	81
Chronic coronary	7	33
Noncoronary	4	31

Sudden death vs the combined groups of chronic and noncoronary patients P < 0 001 (chi-square test)

compared with the chronic coronary and noncoronary patients (Table II)

Lesions of the conduction system Fibrous lesions of the specified grades occurred with similar frequency in the conduction nodes of the sudden death and chronic coronary patients (Tables III and IV) In the noncoronary group fibrosis was less extensive but not significantly so when compared with the sudden death group Patchy fibrosis in the right and left bundle branches in some regions replacing about 50 per cent of the muscle cells was seen in one chronic coronary patient Nonfibrous lesions of the conduction system were seen in 10 of the 46* sudden death cases and in none of the controls Seven of these cases had one or two chronic inflammatory microlesions in the atrioventricular node or bundle of His one had lymphangioendothelioma of the atrioventricular node, one had most of the His bundle replaced by fatty tissue one had myocytolysis [9, 10] of the cells in the sinus and atrioventricular nodes The probability of this difference between the sudden death cases and the controls occurring at random was less than 5 per cent

Myocardial infarcts Four (13 per cent) of the sudden death patients had recent myocardial infarcts (Table V), 37 (79 per cent) sudden death patients had old infarcts, and eight (17 per cent) sudden death patients had no myocardial infarct The frequency of recent, healing and old infarcts was similar among the sudden death and chronic coronary patients The frequency of infarcts in each of the two groups located to the anterior lateral, or posterior wall of the heart was the same as well

*Originally 47 cases Sections from the atrioventricular node were not available in one case

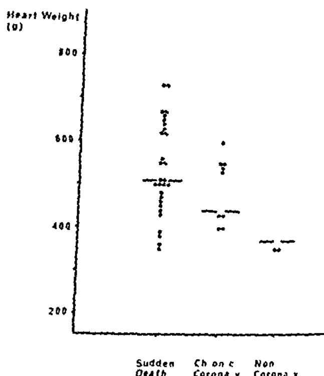


Fig 5 Heart weight (in grams) of the 57 male patients in the three disease groups Median heart weight for each group is indicated Comparison of groups sudden death vs chronic coronary $0.05 < P < 0.10$ sudden death vs noncoronary $P < 0.01$ Wilcoxon rank sum test

Heart weight The hearts of male patients only were compared since the material included only a small number of female patients The sudden death patients had larger heart weights compared with the noncoronary patients, whereas the difference vs the chronic coronary patients was not quite of statistical significance (Fig 5)

Many patients in the chronic coronary and noncoronary groups had wasting diseases which could influence body weight and heart weight [11, 12] Therefore the ratio of heart weight/body weight in the individual patients was compared in the three disease groups This ratio was similar among the sudden death and chronic coronary patients It was somewhat larger in the sudden death patients compared with the noncoronary patients but the difference was not statistically significant

Discussion

Chronic inflammatory microlesions The pathogenesis of the chronic inflammatory microlesions is unknown Small chronic inflammatory lesions of the myocardium have been associated with various infectious or toxic conditions [13, 14] Various agents may have caused the lesions described presently In a previous report, occlusive platelet aggregates were observed in intra

Age related changes in size of the aortic valve annulus in man

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In the course of a study on the effects of the aortic valve on pulsewave transmission [1,2] the need for a method of estimating the degree of aortic valve narrowing in patients of varied age and body size became apparent In earlier studies our group had shown that there was little or no correlation between body surface area and numerous other physiologic measurements including cardiac index Although the changes of aortic valve area with growth are commonly accounted for by comparing them with the estimated body surface area of the subject this practice has surprisingly little scientific basis Dreyer Ray, and Walker[3] showed that there was a correlation of the aortic cross sectional area with surface area and Bazett and co workers[4] showed that there was also a strong influence of age

The size of the aorta in man has been measured in a number of earlier studies Measurements were made from necropsy specimens by Thoma in 1882 Suter[5] in 1897 and Kani in 1910 as well as estimates from radiographs by Smith[6] in 1920 and Vacquez and Bordet in 1928 Data from the above sources were examined with a view toward a re-examination of the contention that aortic cross sectional area correlates significantly with body surface area

Material and methods

Owing to the large number (2 719) of cases examined Suter s data are the most important His subjects are listed by age height weight, and sex. Data in his Table 9 show detailed information on 105 patients from 1½ to 83 years of age with measurements given for aortic diameter at the aortic valve and 1 cm above the aortic valve leaflets One or more items of data were missing on 10 patients leaving 95 patients in whom aortic valve area and surface area could be calculated Kani s data were confined to measurements of the aorta at the valve Kani[7] reported detailed measurements on 207 subjects but his paper listed individual measurements on only 19 subjects ranging from 9 to 58 years of age For both groups patients with significant cardiac disease shown by autopsy findings were omitted from this study These 19 sets of measurements and the 95 of Suter were selected for analysis

Previous studies[1] had shown that the most reliable estimate of body surface area from height and weight was a nomogram developed by Sendroy and Cecchini [2] and this was used to estimate body surface area in this paper Our previous analysis showed that even for this nomogram 21 per cent of the estimated surface areas had an error more than 10 per cent of the measured surface areas Furthermore smaller subjects tended to have lower body surface area estimates and the male body surface area also appeared to be slightly underestimated (Fig 1) In spite of these drawbacks this nomogram is far more accurate than those based on weight alone where 51 per cent of the estimated values had errors greater than 10 per cent of measured surface area values The commonly employed nomogram of Boothby and Sandiford [3] and the modification for pediatric-sized patients by Hannon * both of which are based on the formula of DuBois and DuBois [5] seem to be the most frequently

*This nomogram must rate as the all time high in extrapolation of data since only one measured patient was within the size range of this nomogram

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tions of both the sudden death and chronic coronary cases Since the recent infarcts were few, and no difference existed between the two disease groups one might conclude that acute myocardial infarction did not seem to play a major role in the pathogenesis of sudden coronary death in this series No definite conclusion can be made on this point however, since the technique applied in the study is inadequate for the detection of very early infarcts

Thus the present study demonstrates, in the majority of sudden coronary death patients the following (1) conventional ischemic myocardial lesions (recent and old myocardial infarcts fibrous lesions of the conduction system) in similar quantities as compared with the control group of chronic coronary patients, and (2) chronic inflammatory microlesions prepondering among the sudden coronary death cases indicating a chronic, continuous, and/or possibly relapsing process in the myocardium of these cases

The pathogenesis of the microlesions is unknown but coronary microembolization could explain their presence

Summary

In order to test whether sudden coronary death patients had a more "vulnerable" myocardium compared with other patients morphological lesions of the myocardium and conduction system were examined in a selected autopsy series

Chronic inflammatory microlesions frequently affecting single muscle fibers, predominated among 47 sudden coronary death cases compared with 34 cases with chronic coronary or noncoronary diseases ($P<0.001$) Nonfibrous lesions of the atrioventricular node and the bundle of His also predominated among the sudden death cases ($P<0.05$) Myocardial infarcts of any age as well as relative heart weight (the ratio total heart weight/body weight) did not differ in the sudden coronary death and the chronic coronary patients

The chronic inflammatory microlesions and the nonfibrous lesions of the conduction system predominating among the sudden death cases may signify a vulnerable condition of the myocardium in sudden coronary death

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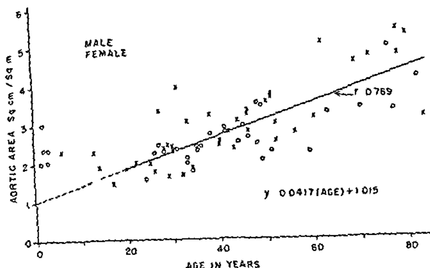


Fig 2 Variation of the cross sectional area of the aortic valve with age The regression line shown is for patients over 20 years of age Patients under 20 years of age in general have higher aortic valve areas per square meter than predicted by the regression equation

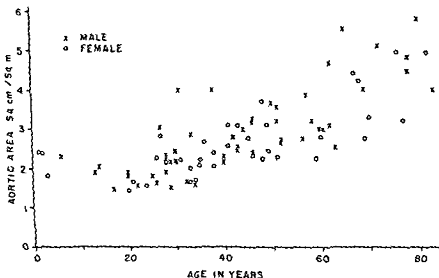


Fig 3 Variation of cross-sectional area of the aorta as measured 1 cm above the aortic valve leaflets As in Fig 2 there is a decline in the area per square meter of body surface area during the first 20 years of life followed by an increase in later life

weight are given in Table I Note that these variables produce correlation coefficients as high as those obtained by using surface area and age (see Figs 1 to 4) Thus there appears to be no advantage to using surface area and then a value corrected for age as opposed to these regression equations where age height and weight may be entered directly

Discussion

It would appear that body surface area as estimated by even the best of the available nomo

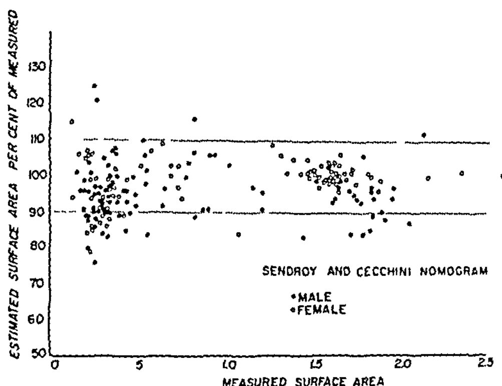


Fig 1 Comparison of the body surface areas of 200 subjects as estimated by the Sendroy and Cecchini nomogram against the surface areas measured by either coating or planimetry (Reproduced by permission from Krovetz L J J Pediatr 67 841 1965)

Table 1 Regression equations for estimating aortic area

Age group	Aortic site	Aortic area* (sq cm)	Correlation coefficient (r)
Under 20 yr	At valve	0 93 + 0 111 (age) − 0 01 (wt)	0 921
	1 cm above valve	−0 42 + 0 018 (ht)	0 910
Over 20 yr	At valve	−4 65 + 0 057 (age) + 0 038 (ht)	0 738
	1 cm above valve	−7 31 + 0 066 (age) + 0 052 (ht)	0 813

*For these equations age is entered in years height (ht) in centimeters and weight (wt) in kilograms

employed but are less accurate than the Sendroy and Cecchini nomogram

Stepwise multiple linear regression analysis was used to derive equations for aortic valve area The independent variables used were age height weight and surface area

Results

Data recalculated from Suter s study expressed as the cross sectional area of the aorta at the aortic valve per meter square of body surface area are shown in Fig 2 Comparable data for the aortic cross sectional area measured 1 cm above the valve are shown in Fig 3 In both instances the aortic cross sectional area declines during the first 20 years of life and increases after this There is a positive correlation for subjects over 20 years between age and cross sectional area per square meter (r = 0 769)

Fig 4 examines the data for the first 20 years of life For this graph the data of Suter and Kani were combined since there did not seem to be any significant differences between them During the first 20 years aortic cross sectional area per square meter of body surface area apparently decreases with age (r = −0 759) Fig 5 illustrates the data for 186 patients in Kani s paper and 2 490 in Suter's paper where the data were grouped In Kani's paper patients under 14 years of age were grouped without regard to sex and patients under 16 years of age were similarly treated in Suter s paper These patients were necessarily omitted from the figure There appears to be a slightly faster rate of aortic dilatation with age for males than for females However in view of the differences in estimation of surface area in males and females ' the significance of these observations is in doubt

Four regression equations for aortic cross sectional area estimated from age height and

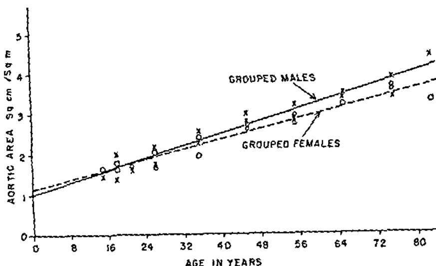


Fig 5 This illustrates grouped data for 207 patients (Kani) and ' 490 patients (Suter[8]) Patients under 14 years of age were grouped without regard to sex by Kani and patients under 16 years of age were similarly treated by Suter[8] these patients were omitted from this graph There appears to be a slightly faster rate of aortic dilatation for males (x) than for females (O) however this is of doubtful significance in view of the differen es in estimation of surface area in males and fema'es (see Fig 1)

but the regression formulas avoid the ambiguity of which surface area formula or nomogram to use As shown previously[3] there are significant differences between various published nomo grams and equations used to estimate body surface area which may result in significant differences in the resultant calculations Finally it might be pointed out that although sex differ ences have been postulated for many of these functions e g cardiac output these are more likely due to differences in the accuracy of esti mating body surface area in the sexes

Summary

Data previously published in the literature regarding the size of the aortic valve in man have been reanalyzed Aortic valve size increases at a slower rate than the surface area of the human body until maturity is reached at approximately 18 to 21 years of age After that age aortic valve size increases nearly linearly with age There appears to be a slightly faster rate of aortic dilatation in males than in females but this may be due to errors in estimating body surface area from only height and weight for obviously different body contours Body surface area thus does not seem to be a good normalizing factor for the aortic valve size and the practice of refer encing aortic valve sizes to the body surface area size should be discontinued Alternate forms of using linear regression equations are reported and would appear to be preferable

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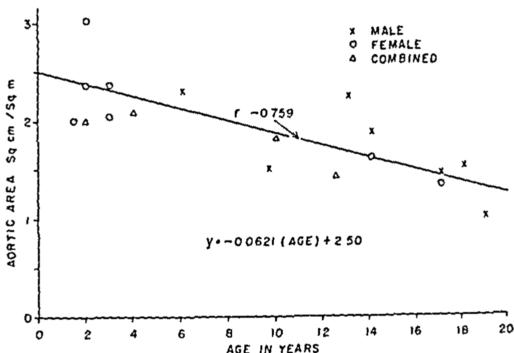


Fig 4 Variation of cross sectional area of the aortic valve in the first 20 years of life The triangle refers to groups of patients where sex was not stated The aortic valve area per square meter body surface area declines during this time interval

grams increases at a faster rate than does the aortic valve size up to the age of maturity After age 20, the aorta and the aortic valve ring begin to dilate paralleling the changes in modulus and elasticity [16, 17] Thus, a decrease in elasticity of the major arterial vessels, which is a primary sign of arterial aging begins as soon as adulthood is reached With increasing age, the volume of the thoracic aorta increases and there is considerable weakening of the wall [17] These volume increases are paralleled by a decrease of distensibility of the aortic wall and an increase in tangential wall stress Interestingly enough no significant changes with age in the relative amounts of the fibrous proteins collagen and elastin, have been found in the walls of the arteries [18] Learoyd and Taylor[16] conclude that some qualitative deficiency occurs in the wall elements with aging which causes a reduction of the tensile strength of the wall with age and permits dilatation of the thoracic aorta

In 1839 Rameaux and Sarrus proposed that it is Nature's aim to make the heat production of large and small animals proportional to their respective surface areas [19] This hypothesis soon became known as the law of surface area ' The concept of basal or standard metabolism i e caloric heat per square meter was introduced largely in order to compare subjects of different sizes but comparable activities In later years proponents extended the surface area law to other physiologic functions thought to be related to heat production or metabolic turnover It has been suggested that surface area was related not only to body metabolic rate but also to cardiac output, oxygen consumption, renal plasma flow, organ size and virtually every other measureable physiologic or anatomic variable

In previous papers [3, 4] we examined the relationship of body surface area to a number of these variables, including caloric production oxygen consumption, and cardiac output Although there is a trend for most physiologic functions to increase with increasing size of the subject, relating the function to body surface area or indeed to any single measurement of body size offers only a crude index of normality A better way of defining normal values in relation to size is the use of the multiple regression equations [4] Such equations have two drawbacks namely (1) several terms and calculations are necessary and (2) a separate equation is required for each variable The primary advantage, however, is that the items entered into the regression equation can be readily determined, such as height and weight These are also needed for surface area estimates

Effects of age on responses to isometric exercise

Isometric handgrip in noninvasive screening for cardiovascular disease

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Exercise stress tests have been generally used to detect cardiac malfunction There are two basic kinds of exercise challenge which are most commonly used One is rhythmic exercise which utilizes such equipment as a treadmill bicycle ergometer or set of steps and produces increased heart rate (HR) cardiac output and systolic blood pressure with little or no increase or even decrease in diastolic blood pressure The other type isometric exercise usually isometric hand grip (IHG) tends to produce less increase in heart rate and cardiac output but marked increases in both systolic and diastolic pressures usually without changing systemic vascular resistance at least in normal subjects

Because of simplicity the IHG test has attracted the attention of the cardiologist Isometric exercise must be performed at a grip strength sufficient to impose an acutely increased afterload on the left ventricle It has been reported that systolic time intervals are sensitive enough to reflect those changes in ventricular performance produced with IHG

The present study was performed to detect any difference in responses to IHG between normal subjects and age matched subjects with hypertensive heart disease (HHD) and coronary artery disease (CAD) These older normal subjects were also compared to young normal adults with regard to cardiocirculatory responses to IHG Our aims were to assess the adequacy of IHG as a screening test for heart disease and to investigate any age related changes Because other investigations have demonstrated little or no change in cardiac responses at low levels of IHG we designed a protocol which required maximal or near maximal IHG

Material and methods

Studies were performed on 30 elderly male subjects who were ambulatory participants of the Framingham Heart Study and subclassified into three groups of 10 subjects each old normals (ON age 54 to 78) hypertensive individuals (HHD age 58 to 77) and subjects with coronary artery disease (CAD age 59 to 79) In addition 10 normal young male adults (young normals or YN age 23 to 31) were also studied

The old normals were those who had been normotensive and free from CAD or other disease over 22 years of periodic examination The hypertensives were defined as subjects who had persistent cuff blood pressures exceeding 140/90 mm Hg Individuals in the coronary disease group had a history of myocardial infarction documented by ECG the appropriate laboratory examinations and/or typical anginal attacks No subjects had been taking cardiotonic agents

Simultaneous ECG (Lead II) phonocardiogram and carotid pulse tracing were recorded in the supine position at a paper speed of 50 mm per second on a Schwarzer No 622 6 channel recorder

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CARu Time from Q to the onset of the rapid portion of the carotid (CAR) upstroke

II_A Time from Q to the first high frequency (aortic) component of the second heart sound

CAR_{in} Timing of the carotid incisura

Calculations

Pulse transmission time (PTT) $CAR_i - II_A$

Isovolumic contraction time (IVCT) CAR − PTT − I_m or PEP − I_m

Pre ejection period (PEP) CAR − PTT

Left ventricular ejection time (LVET) CAR_i − CAR

Left ventricular ejection time index (ETI) LVET + 1 2 hr

Ratio of pre ejection period to ejection time (PEP/LVET)

The old normals (ON) were the reference group Systolic time intervals at rest and changes in response to IHG of the ON were compared with those of subjects with HHD and those with CAD Comparison was also made with those of the normal young male subjects (YN) As reported in several studies' no subject in our series suffered hazardous complications dysrhythmias or angina during IHG All subjects were coached to avoid the Valsalva maneuver and probably were free from it since respiration was observed shortly after initiation of IHG Blood pressure measurement during IHG was not performed since the IHG test was inserted into an established patient flow pattern and this investigation was aimed at determining the value of effects on systolic intervals as a screening method Further more significant increases in systolic and diastolic blood pressures are uniformly anticipated during IHG

Blinding procedure Responses were measured without knowledge of the clinical status of the patients and old normals

Statistical handling Changes from control data were determined for all measurements The t test for independent data was applied to compare responses between old normals (which was the reference group) and each of the other three groups

Results

Table I comprises the data on the entire study group with mean values standard errors of the mean and P values for comparisons between ON and HHD subjects, between ON and CAD subjects, and between ON and YN

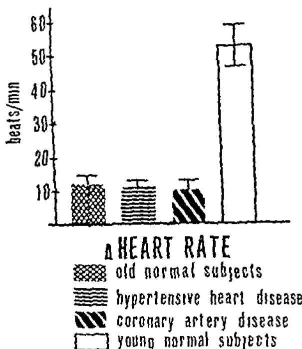


Fig 1 Top Heart rate changes from control during maximal or near maximal IHG Bottom Code for subgroups (applicable to all illustrations)

1 ON vs HHD and CAD

Control (resting) data Resting recordings did not show any difference in heart rate and systolic time intervals except for Q Im which was significantly shorter in HHD ($p < 0.05$) Control PTT was significantly shorter in CAD ($p < 0.05$)

IHG There were no differences in responses to the isometric exercise for ON vs HHD and ON vs CAD In each of these groups isometric exercise resulted in an increased HR (Fig 1) and PEP/LVET (Fig 2) prolonged PEP and IVCT (Fig 3) shortened LVET (Fig 4) and PTT (Fig 2) and almost no change in ETI (Fig 4) and Q Im (Fig 3)

2 ON vs YN

Control data There were no differences in HR and STI in resting recordings except for PTT which was significantly shorter in the old normals ($p < 0.001$) Based on our previous studies STIs were all normal in both groups[11]

IHG there were clear differences in responses to IHG

Increase in HR was much more prominent in YN vs ON (+ 51 6 vs + 11 6) beats per minute $P < 0.001$) (Fig 1) PEP and IVCT decreased in young individuals during IHG but increased in

Table I Data on entire study group

Variables	Control ± SE	P (vs ON)	HHG ± SE	Change ± SE	P (vs ON)
HR beats/min					
ON	68 3 ± 2.6		80 1 ± 2 6	+11 6 ± 2 6	
HHD	77 1 ± 5 0	NS	88 2 ± 4 7	+11 1 ± 2 1	NS
CAD	69 0 ± 4 5	NS	78 8 ± 4 6	+9 8 ± 2 0	NS
YN	69 4 ± 4 6	NS	120 8 ± 3 9	+51 6 ± 5 7	<0 001
Q Im (msec)					
ON	52 2 ± 3 0		50 8 ± 3 0	−2 1 ± 1 9	
HHD	44 2 ± 2 1	<0 05	45 1 ± 1 4	+0 9 ± 1 7	NS
CAD	53 7 ± 1 7	NS	53 1 ± 5 1	−0 6 ± 1 1	NS
YN	60 5 ± 3 1	NS	57 5 ± 2 6	−3 0 ± 1 3	NS
PTT (msec)					
ON	27 1 ± 2 6		22 7 ± 1 8	−5.5 ± 2.2	
HHD	24 3 ± 2 1	NS	22 3 ± 2 2	−2 0 ± 2 1	NS
CAD	20 7 ± 1 3	<0 05	17 6 ± 1 9	−3 1 ± 2 1	NS
YN	43 7 ± 1 4	<0 001	35 7 ± 1 7	−8 0 ± 1.9	NS
IVCT (msec)					
ON	43 7 ± 5 1		50 3 ± 5 8	+8 1 ± 2 2	
HHD	41 9 ± 4 0	NS	49 9 ± 4.3	+5 0 ± 1 8	NS
CAD	47 7 ± 5 5	NS	57 6 ± 5 6	+9 9 ± 2 2	NS
YN	39 0 ± 1 9	NS	25 2 ± 1 9	−13 8 ± 3 4	<0 001
PEP (msec)					
ON	95 9 ± 4 8		101 1 ± 5 5	+6 2 ± 1 7	
HHD	89 1 ± 4 2	NS	95 0 ± 4 3	+5 9 ± 2.5	NS
CAD	97 4 ± 2 8	NS	110 7 ± 5 7	+9 3 ± 2 5	NS
YN	97 6 ± 4 5	NS	86 6 ± 4 6	−11 0 ± 3 7	<0 001
LVET (msec)					
ON	282 7 ± 8 7		276 6 ± 7 0	−6 5 ± 4 1	
HHD	276 6 ± 11 3	NS	263 1 ± 10 3	−13.5 ± 5 1	NS
CAD	273 4 ± 11 6	NS	266 9 ± 12 1	−6 5 ± 3 5	NS
YN	296 6 ± 7 1	NS	233 0 ± 7 5	−63 6 ± 9.9	<0 001
ETI (msec)					
ON	364 7 ± 6 2		371 8 ± 4 8	+5 1 ± 3 4	
HHD	369 0 ± 6 7	NS	367 6 ± 7 4	−1 4 ± 5 5	NS
CAD	319 3 ± 7 2	NS	361 6 ± 7 8	+5 3 ± 3 6	NS
YN	378 5 ± 4 0	NS	378 1 ± 6 0	−0 4 ± 7 3	NS
PEP/LVET					
ON	0 331 ± 022		0 370 ± 025	+ 034 ± 012	
HHD	0 329 ± 025	NS	0 369 ± 027	+ 040 ± 016	NS
CAD	0 396 ± 013	NS	0 434 ± 052	+ 048 ± 013	NS
YN	0 339 ± 013	NS	0 360 ± 013	+ 021 ± 018	NS

or a Hewlett Packard No 4560 8 channel recorder After resting recordings were obtained all subjects were first asked to squeeze a handgrip dynamometer as hard as possible The degree of this isometric contraction was recorded as the maximum voluntary contraction (MVC) of the subject For this investigation, subjects were asked to try to sustain 100 per cent MVC for at least 30 seconds Some subjects found this difficult to maintain Therefore exercise was performed under the close observation of a physician and nurse with polygraphic recording only during the time when the subject exceeded 75 per cent MVC and maintained it for half a minute This criterion resulted in rejection of additional subjects who could not achieve and maintain at least this level of exertion With the use of standard definitions and calculations as previously reported[10,11] systolic time intervals were determined as follows

Definitions

Cycle length The R R interval of the ECG, expressed in milliseconds

Q Initiation of the QRS complex in Lead II, whether a Q wave or the beginning of the R upstroke

Im Time from Q to the first high frequency ("mitral) oscillation of the first heart sound

MVC in the supine position it causes brisk responses in HR BP and STI while at less than 50 per cent these are much more gradual and of less magnitude[5] Therefore it appeared that for screening by STIs IHG should be done at maximum or at least near maximum levels of exertion

In this study despite maximum or near maximum challenges there were no differences in changes in STIs between old normals and the HHD or CAD groups It is possible that STI measurements could not detect small differences in left ventricular performance occurring during the IHG test or that there was actually no demonstrable difference in left ventricular function between our group of older normal subjects and the age matched patients The STIs have been extensively studied by many investigators in various clinical situations and it is generally accepted that STIs have a good correlation with ventricular hemodynamics [2] Therefore the similarity of STI and HR responses during IHG suggests that significant differences in left ventricular performance were not provoked by IHG among our old groups Furthermore since our old individuals were all ambulatory subjects it was not entirely surprising that resting STIs in these groups were within normal limits (Table I) Although there were no differences between ON vs HHD and CAD groups when the old normals were compared with young normals significant differences in their response to IHG were demonstrated In the YNs heart rate was markedly more accelerated and owing to decreased IVCT the PEP decreased This was in striking contrast to the uniform increase in IVCT and PEP in all three older groups—a clear directional difference It has not been our practice to correct PEP for HR because there is stronger recent evidence against this practice [1] Pure rate change by atrial pacing does not significantly change individual pre-ejection periods while the effects of inotropic influences themselves increase HR and decrease PEP Thus rate correction would mask inotropic effects Moreover a recent computerized study of STIs in a 100 patient series showed no significant interindividual relationship between PEP and HR in resting subjects [1]

Experimental studies disclosed that the aging process is physiologically associated with depressed contractility (e g decreased ATPase activity) and reduced physiologic responsiveness to

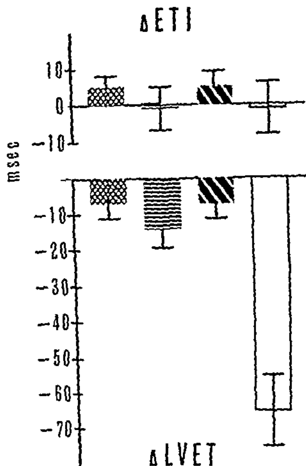


Fig 4 Top Change in ejection time index (Δ ETI) during IHG Bottom Change in left ventricular ejection time (Δ LVET) during IHG Code for subgroups as in Fig 1

various stresses [5] resulting for example in decreased maximum HR on exercise with increased age [6,16]

We observed significantly less increase of HR in ON as compared to YN Since increase in HR with IHG is mainly caused by sympathetic preponderance resulting from rapid withdrawal of vagus influence this result is consistent with decreased sympathetic tone in our old normals This can be of central and peripheral origin (heart and muscle respectively) and accounts for less increase of HR than that in the YN

PEP, comprised of IVCT and Q Im has an inverse relationship with the rate of rise of left ventricular isovolumic pressure (dP/dt) [22,2] According to Grossman and co workers[19] the normal physiologic response to isometric exercise includes increased myocardial contractility observed as improvement of Vmax and dP/dt Accordingly shortening of PEP is consistent with

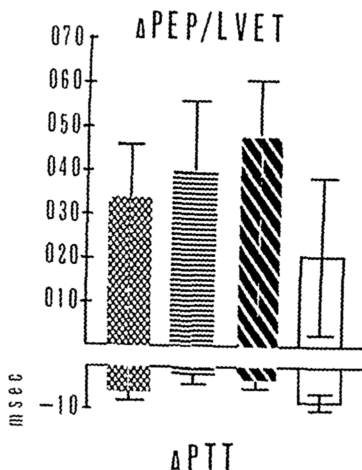


Fig 2 Top Changes in ratio of pre ejection period to ejection time (Δ PEP/LVET) during IHG Bottom Changes in central pulse transmission time (Δ PTT) during IHG Code for subgroups as in Fig 1

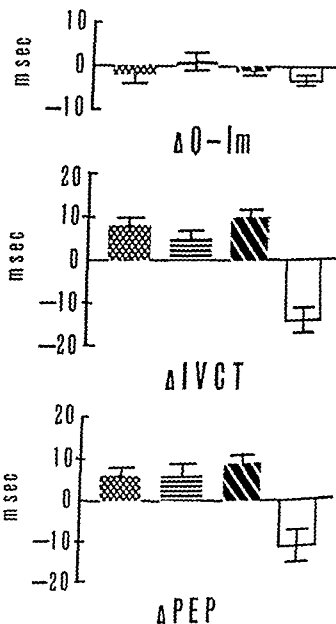


Fig 3 Top to bottom Changes during IHG in timing of mitral component of first heart sound (Δ Q Im) isovolumic contraction time (Δ IVCT) and pre ejection period (Δ PEP) Code for subgroups as in Fig 1

old normals (Fig 3) These changes from control for YN vs ON were statistically significant ($p < 0.001$ each) Shortening of LVET was much more marked in young normals ($p < 0.001$) Comparison of changes from control for ON vs YN in Q Im ETI, PEP/LVET were not statistically significant although PEP/LVET (Fig 2) in young normals had much wider variability with a tendency to increase less with IHG

Discussion

In young normal individuals IHG when performed at more than 50 per cent of the MVC causes prompt and significant responses in HR BP, and systolic time intervals [5] Increases in HR and mean BP usually without increased systemic resistance have been generally observed in previous studies [1, 19]

The increase in HR during IHG is mainly caused by rapid withdrawal of vagal influences on the heart[16] and partly by adrenergic nervous influences of central origin[1] and reflexes in the muscle spindle mechanoreceptors [1, 17] Increase in the BP is considered to result from a reflex from the contracting muscle, where blood flow is markedly impeded by the sustained muscle contraction and also may be due to moderate increases in cardiac output on some occasions [1, 19, 20]

The normal physiologic response to adequately stressful IHG includes a major increase in HR and left ventricular myocardial contractility without significant changes in the left ventricular filling pressures [18] For the diseased heart increased ventricular performance induced by IHG has been reported to be mediated via increased contractility, but also via the Frank Starling mechanism the latter being more important in subjects with diminished inotropic reserve [19] A report from our laboratory[5] showed that when IHG is performed at from 50 to 100 per cent of the

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increased contractility during near maximal isometric exercise

Acutely induced increases in afterload by themselves cause prolongation of PEP and LVET [..] The shortening of PEP with little change of ETI observed in the young normals is considered to be brought about by significantly increased myocardial contractility which could well overcome this effect of afterload, while in old subjects with reduced adrenergic tone it could not

LVET shortens as HR increases this rate effect is removed by calculating the ETI [39,40] Since there were no significant changes in ETI with IHG shortening of LVET in all our groups was a function of increased HR PEP/LVET has a high negative correlation with ejection fraction and stroke volume [23,24] Helfant DeVilla, and Meister[1] reported that in normal subjects in supine position IHG caused increased cardiac output with little change in stroke volume and LVEDP while in abnormal subjects IHG caused significantly decreased stroke volume and markedly increased LVEDP with little change in cardiac output Therefore increased PEP/LVET in old normals may result from decreased ejection fraction and stroke volume in addition to a less significant increase or an actual decrease in myocardial contractility

Resting PTT was observed to be significantly shortened in ON as compared to YN, and much shorter in the CAD group, which indicates an age related development of arterial rigidity accentuated in atherosclerotic patients, with a consequent increase in pulse wave velocity Prolongation of the Q Im interval in hypertensive patients which was observed by Weissler, Leonard, Warren[41] and Sakamoto, Kaito and Ueda [42] was not observed in our hypertensive group We have no explanation for this discrepancy, except the possibility of hyperfunction in ambulatory hypertensives as compared with hospitalized hypertensives

In summary, in this study, STIs with IHG did not disclose any difference between elderly normals and patients with HHD or CAD although it elicited significant qualitative and quantitative differences in STIs between old and young normal subjects Therefore the IHG test even at 100 per cent MVC does not seem to be an adequate stress test in screening for heart disease by STI in older subjects

Summary

Isometric handgrip (IHG) imposes an acutely increased afterload on the left ventricle Utilizing systolic time intervals we studied various responses to IHG, measured as changes from resting values with near maximum IHG in old normal (ON) subjects, young normal (YN) subjects, and old patients with hypertensive heart disease (HHD) and patients with coronary artery disease (CAD) There were no differences in responses to IHG between ON and patients with HHD or patients with CAD However there were clear differences between the responses of ON and YN subjects Increase in heart rate (HR) was much more prominent in YN (ON vs YN = +11 6 ± 2 6 vs +51 6 ± 5 7 beats per minute $p < 0\,001$) Pre ejection period (PEP) end isovolumic contraction time (IVCT) increased in ON but decreased in YN (PEP + 6 2 ± 1 7 vs −11 0 ± 3 7 msec, $p < 0\,001$, IVCT +8 1 ± 2 2 vs −13 8 ± 3 4 msec $p < 0\,001$ Shortening of LVET was much more marked in YN (− 6 5 ± 4 1 vs −63 3 ± 9 9 msec $p < 0\,001$) but this was entirely due to the HR differences since there was no difference in ejection time index (+ 5 1 ± 3 4 vs −0 4 ± 7 3 msec $p > 0\,5$) IHG produced no significant differences between ON and YN in the timing of the 'mitral' component of the first heart sound (q Im) in the ratio PEP/LVET, or in pulse transmission time (PTT) By contrast resting control PTT was markedly short in ON, especially those with CAD Resting PTT in ON was 27 1 ± 2 6 msec in YN 43 7 ± 1 4 msec in CAD patients 20 7 ± 1 3 msec We conclude that even near maximal IHG does not seem to be an adequate noninvasive screening test for cardiovascular disease in that age alone seems to have the most significant influence on the responses

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Table I Change in serum lipids and protein bound carbohydrate (in milligrams per 100 ml of serum)*

	Control mg/100 ml	Day 1		Day 2		Day 10	
		Mg/100 mL	% of control	Mg/100 ml	% of control	Mg/100 ml	% of control
Protein bound carbohydrate	109 ± 1.5	127 ± 5.0	117	134 ± 4	123	166 ± [illegible]	152
		p < 0.01		p < 0.001		p < 0.001	
Cholesterol	176 ± 6	274 ± 12	156	268 ± 12	15-	236 ± 9	134
		p < 0.001		p < 0.001		p < 0.001	
Triglyceride	85 ± 5	154 ± 24	181	173 ± 1[illegible]	204	173 ± 22	204
		p < 0.01		p < 0.001		p < 0.001	

A l l es are ± S E M All p ues re compared to ontrol

serum obtained from Behring Diagnostics Somerville N J All samples were run against three provided standards for each glycoprotein The precision of these determinations when compared to serum of known concentrations was found to be within ± 4 per cent The results of glycoprotein determinations when repeated on different days were found to show no statistically significant variation with Student's t test

Mean values on hospital days 1 2 and 10 were compared to controls with Student's t test for independent samples and p values were determined

Results

Table I shows that there is an elevation of total serum protein bound carbohydrate when compared to the controls which further increases during evolution of the infarction By day 10 the protein bound carbohydrate had risen to 166 mg per 100 ml compared to the control value of 109 ($p < 0.001$) In contrast the cholesterol value was significantly elevated on admission but by day 10 approached the accepted normal range although still significantly greater than the control value The triglyceride values also were significantly elevated on admission and continued to be abnormal during the study Lipoprotein electrophoresis showed no abnormalities in the normal controls While four patients did show a slight decrease in the beta band during the course of the study lipoprotein electrophoresis on the infarction patients revealed no consistent deviations from normal at the time of admission nor by day 10 of hospitalization

Table II shows the results of the individual serum glycoprotein analyses No change was seen in the IgA or α macroglobulin when compared to the controls In contrast a significant decrease in α HS glycoprotein occurred on days 2 and 10 following infarction There was also a slight and transient decrease in Gc globulin on day 2 IgG was significantly lower on admission but by hospital day 10 had increased to the value of the controls IgM ceruloplasmin and hemopexin did not show significant increases until day 10 after infarction The greatest change of all of the serum glycoproteins occurred in IgM which was 794 per cent of the control values on day 10 The α_1 antitrypsin haptoglobin and α acid glycoprotein were significantly elevated over normal on admission and continued to increase during the course of the study Transferrin also was significantly increased on admission but did not appear to change further The β glycoprotein I was slightly elevated on admission but by hospital day 10 was not significantly different from the controls All three components of complement β_1A globulin β E globulin and β glycoprotein II were significantly elevated on admission and continued to rise

Discussion

On admission to the hospital patients with acute myocardial infarction already have an elevation in serum protein bound carbohydrate which increases further during the succeeding 10 days Increases in protein bound carbohydrate have likewise been shown to occur in a variety of acute and chronic disease states * Although this elevation seen on admission might be entirely due to myocardial infarction it could be related in part to either chronic atherosclerotic cardiovascular disease or the modest hyperlipidemia which the subjects manifested

To account for the increase in protein bound

Serum lipids and glycoproteins in acute myocardial infarction

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Elevations of serum protein bound carbohydrate have been described previously in a number of unrelated diseases including cancer[1] acute infections and inflammatory states[2] diabetes mellitus[3] chronic arteriosclerotic cardiovascular disease[4] acute myocardial infarction[5] and hyperlipidemic subjects of all types with or without clinically apparent vascular disease[6] The elevation of protein bound carbohydrate in hyperlipidemic subjects has been shown to be due to a glycoprotein response characterized by elevations in haptoglobin hemopexin α_1 acid glycoprotein, and ceruloplasmin and no change in 10 others This profile is different from that described in either cancer patients[7] or diabetics[8]

Prior studies of the changes in specific glycoproteins following acute myocardial infarction[9,10] have not included all of the measurable glycoproteins In addition because of the known association of hyperlipidemia with both atherosclerosis and hyperglycoproteinemia, any relationship between abnormalities in serum glycoproteins and serum lipoproteins needs to be explored Therefore, this study was undertaken in order to quantitate the precise glycoprotein changes occurring in acute myocardial infarction It was anticipated that a glycoprotein profile different from that previously reported in other disease entities would be found

Method

Venous blood samples were obtained from 10 patients admitted to the Hahnemann Medical College and Hospital Coronary Care Unit with acute myocardial infarction Patients having any prior chronic disease with the exception of possible atherosclerotic cardiovascular disease were not included nor were patients who developed complications of infarction The clinical diagnosis in each case was corroborated by both typical electrocardiographic (ECG) and enzyme changes Blood for this study was drawn along with routine studies on admission (day 1) and fasting on the second and tenth hospital days Control values were obtained from 16 sex and age matched normal subjects

Both cholesterol and triglycerides were determined on serum by automated methods previously described[11] Lipoprotein electrophoresis was performed on plasma anticoagulated with EDTA with agarose plates obtained from Bio Rad Laboratories The criteria of Frederickson, Levy, and Lees[12] for abnormal plasma lipoproteins, cholesterol and triglycerides were adopted for this study

Measurement of total serum glycoproteins was accomplished by determining serum protein bound neutral sugars This was performed spectrophotometrically by the phenol sulfuric method[13] using a standard composed of galactose mannose and fucose in the ratio of 5 5 1

Quantitation of individual serum glycoproteins was performed by standard radial immunodiffusion[14] on plates containing monospecific anti

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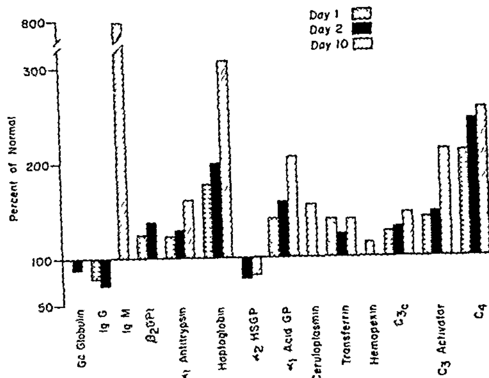


Fig 1 Profile of glycoprotein (GP) changes during the course of acute myocardial infarction as a per cent of normal controls

the controls in this study the cholesterol concentration decreased during the course of hospitalization as has been previously reported[1] The slight upward trend in triglyceride values is also in agreement with other studies[15] This might be related to a relatively increased carbohydrate intake both dietary and intravenous in patients on a low fat diet.

In an earlier study of the protein changes in myocardial infarction Agostoni and co workers[9] reported increases in α antitrypsin haptoglobin α acid glycoprotein and β A globulin Their results were felt to be part of the typical acute phase reaction of inflammation but they did not study any other glycoprotein changes The acute phase" reaction of infection or inflammation has actually been characterized by simultaneous rises in α antitrypsin α acid glycoprotein ceruloplasmin and haptoglobin as our patients showed

In addition the increases seen in IgM complement proteins and hemopexin and the slight transient increase in β_2 glycoprotein I may all be part of the acute phase reaction since none of these proteins has been well studied in acute inflammatory conditions In addition α_2 HS glycoprotein and IgG which were found to decrease in this study also have not previously been studied as part of the acute phase reaction Decreases in transferrin have previously been reported[16] as part of the acute phase reaction and the levels of transferrin throughout this study although higher than the controls did show a decrease on hospital day 2 as compared to admission values This glycoprotein profile is thus somewhat similar to that reported previously for the acute phase reaction but until the latter is further characterized it is impossible to determine whether any of these changes could be specific for myocardial infarction

In a previous study of patients having severe endogenous hyperlipidemia[4] there were elevations of α acid glycoprotein ceruloplasmin haptoglobin hemopexin and all three complement components but no increases of IgM α_1 antitrypsin β_2 glycoprotein I or transferrin or decreases in IgG or α HS glycoprotein Thus it appears that the glycoprotein profile in acute myocardial infarction is somewhat different from that reported in chronic hyperlipidemic states While the patients in our study did show a definite elevation of both triglyceride and cholesterol on admission when compared to the normal

Table II Glycoprotein changes during acute myocardial infarction (in milligrams per 100 ml of serum)*

Glycoprotein	Control (mg/100 ml)	Day 1 Mg/100 ml	Day 1 % of control	Day 2 Mg/100 ml	Day 2 % of control	Day 10 Mg/100 ml	Day 10 % of control
IgA	221 ± 18	172 ± 21 NS	78	182 ± 25 NS	82	240 ± 35 NS	109
α Macroglobulin	252 ± 18	236 ± 26 NS	94	215 ± 20 NS	97	242 ± 22 NS	96
α HS G P	59.8 ± 2.2	52.1 ± 4.3 NS	87	47.2 ± 2.7 < 0.01	79	48.7 ± 3.0 < 0.01	81
C globulin	27.2 ± 0.7	25 ± 1 NS	92	24 ± 1 < 0.02	68	27 ± 1 NS	99
IgG	1 252 ± 87	988 ± 49 < 0.02	79	904 ± 54 < 0.01	72	1 210 ± 158 NS	95
IgM	170 ± 30	384 ± 248 NS	227	503 ± 337 NS	236	1 350 ± 462 < 0.02	94
Ceruloplasmin	29.1 ± 2.7	31.8 ± 2.9 NS	109	31.7 ± 7.7 NS	119	44.9 ± 5.7 < 0.02	154
Hemopexin	74.6 ± 1.3	80 ± 3 NS	107	79 ± 2 NS	106	85 ± 4 < 0.05	114
α antitrypsin	236 ± 11	292 ± 20 < 0.05	124	300 ± 13 < 0.001	127	381 ± 32 < 0.001	161
Haptoglobin	142 ± 7	250 ± 37 < 0.01	176	281 ± 42 < 0.01	198	433 ± 87 < 0.01	305
α acid G P	70 ± 2.4	98 ± 9 < 0.01	140	110 ± 10 < 0.001	157	143 ± 13 < 0.001	204
Transferrin	229 ± 9	315 ± 19 < 0.001	139	279 ± 17 < 0.02	122	317 ± 31 < 0.02	138
β C PI	17.5 ± 0.5	22.0 ± 1.4 < 0.01	126	23.8 ± 2.9 < 0.05	136	20.9 ± 1.6 NS	119
β A globulin	77 ± 2.2	97 ± 6 < 0.01	126	100 ± 6 < 0.01	130	112 ± 6 < 0.001	146
β glycoprotein II (C activator)	16.6 ± 0.99	23.3 ± 1.5 < 0.01	140	24.2 ± 1.1 < 0.001	146	34.7 ± 4.1 < 0.001	209
β 1 globulin	259 ± 1.6	54 ± 9 < 0.01	209	62 ± 8 < 0.001	239	65 ± 8 < 0.001	251

Mean values are ± S E M All p values are compared to controls

carbohydrate after myocardial infarction, there was not a generalized rise in all of the glycoproteins studied Rather eight specific glycoproteins were found to be increased on admission and 10 were increased by day 10 of the study when compared to normal controls In contrast one protein IgG, was significantly depressed on admission and on day 10 another protein α_2 HS glycoprotein was decreased This profile of glycoprotein response is depicted in Fig 1

The results also showed that the serum lipids and serum glycoproteins changed independently While on admission cholesterol and triglycerides were both significantly elevated above the level of

Experimental and laboratory reports

Nitroglycerin treatment following experimental coronary occlusion

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The effectiveness of nitroglycerin (TNG) in relieving angina pain is generally accepted[1] Although a few authors claim TNG is of no benefit in relieving angina[2,3] numerous clinical studies indicate that TNG provides relief from angina improves exercise tolerance and relieves symptoms of myocardial ischemia[4-6] The continuing discussion regarding the use of TNG has been concerned with the duration of its effectiveness the mechanism of action and its use in patients suffering acute myocardial ischemia

Most studies indicate that TNG when administered sublingually exerts its maximum action within three minutes with some claims of continuing action for another two to ten minutes[1,9,10] Intravenous and intra arterial injection of TNG results in an even shorter duration action[1,11] Under experimental conditions prolonged action of TNG has been achieved by continuous intravenous infusion[3,14] Attempts to prepare long acting nitrates have not been very successful[5,6] although Krantz[15] reports controlled release TNG exhibits the same pharmacodynamic action as sublingual administration but over an extended period of time

Even though TNG is commonly used for the relief of angina some investigators assert that it is contraindicated in cases of acute myocardial infarction. It is suggested that the hypotension which results from TNG may decrease myocardial perfusion pressure and blood flow increase heart rate and increase the myocardial ischemia[16] Assuming that hypoxia is a potent coronary vasodilator TNG may even divert blood from the ischemic areas by producing vasodilation of those blood vessels not already maximally dilated by hypoxia[17] However experimental studies have shown that TNG treatment following coronary artery occlusion raises fibrillation threshold[4] decreases mortality[9] increases cardiac output slightly[20] and reduces the severity of the infarction[3]

The present experiments are designed to provide an experimental basis for evaluating whether TNG has hemodynamic and metabolic effect beyond the reported three minutes and for determining the effect of TNG in animals with coronary artery occlusion

Methods

Experimental studies were carried out in male mongrel dogs weighing 20 to 30 kilograms The animals were anesthetized with sodium pentobarbital (30 mg per kilogram) The coronary occlusion technique was modified from that used by Ribeilima[21] Catheters were inserted with fluoroscope visualization as follows (1) Femoral vein for measurement of pressures in the right atrium (RA) right ventricle (RV) and pulmonary artery (PA) (2) Femoral artery for measuring left atrial pressures and obtaining arterial blood samples (3) Jugular vein with placement in the coronary sinus for withdrawing venous blood samples and injecting heparin (100 units per kilogram) and maintainance doses of anesthetic (4) Common carotid artery for measuring left ventricle (LV) and aortic (AO) pressures and also withdrawing blood for cardiac output determinations Coronary occlusion was achieved by placing this catheter in the circumflex branch of the left coronary

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controls these values were not greatly elevated when compared to published upper limits of normal[12]

Further investigation needs to be done to determine the precise mechanism for glycoprotein elevations in myocardial infarction, but it might be related to substances released from the infarcted tissue which selectively increase the synthesis of certain proteins or decrease their degradation

The complement increases observed may simply be part of the acute phase reaction but there is some evidence interrelating abnormalities in complement with atherosclerosis[1] and it is conceivable that the increases in complement observed are specific for an atherosclerosis related process

In addition the profile of glycoprotein response could be used to develop a diagnostic test for acute myocardial infarction Detection of a significant increase of those glycoproteins shown to be elevated during myocardial infarction might be useful as a corroborative diagnostic test in the absence of any acute inflammatory conditions

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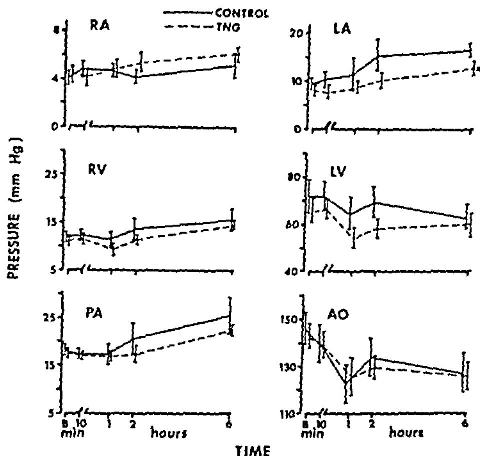


Fig 1 Mean blood pressures following embolization of the left coronary artery in a control group (n = 6) and nitroglycerin (TNG) treated group (n = 10) of dogs In the TNG treated group sublingual TNG (0 2 mg) was administered 5 to 10 minutes prior to each measurement time represented on the abscissa as baseline (B) 10 minutes before embolization (10 min) and 1 2 and 6 hours after embolization The ordinate is the mean blood pressure (mm Hg) RA = right atrium RV = right ventricle PA = pulmonary artery LA = left atrium LV = left ventricle AO = aorta The vertical lines represent ± SE An asterisk indicates a significant difference ($P < 0.05$) from the corresponding control value

artery and injecting 1 1 mm diameter stainless steel ball bearings (3 per kilogram) Blood pressures were measured with a Statham P23D pressure transducer and recorded with a Sanborn Model 150 polygraph recorder Cardiac output was measured by dye dilution using Cardiogreen dye and a Gilford 105 IR densitometer with a Lexington Instruments cardiac output computer Stroke volume was calculated from cardiac output and heart rate data Vascular resistance was calculated from arterial-atrial pressure differences divided by cardiac output (l per minute) and expressed as Wood units The ECG was recorded using Lead II

Blood samples were withdrawn from the left atrium and coronary sinus for studies of enzymes blood gases acid-base characteristics, and metabolic substrates Analysis procedures were the same as used previously [18]

Two groups of animals were used in these experiments (1) The control group of six animals in which the circumflex branch of the left coronary artery was occluded by injection of stainless steel ball bearings and (2) the experimental group of ten animals with coronary artery occlusion and TNG treatment TNG was administered by placing 0 2 mg of Nitrostat sublingually TNG was administered five times ten minutes after obtaining baseline measurements immediately after embolization and again one hour two hours and six hours after occlusion

All hemodynamic parameters were measured and blood samples withdrawn for analysis prior to embolization (Base) ten minutes after baseline measurements one two and six hours after embolization In each case of TNG treatment the blood samples were withdrawn five minutes after administering the TNG and hemodynamic parameters were measured during the next 5 to 10 minutes The data from the period after embolization was compared with the base values and the data from the TNG treated animals compared

Table I Comparison of hemodynamics in TNG treated (N = 10) and control dogs (N = 6) before and after coronary artery occlusion

		Before occlusion		Time after occlusion		
		Base† ± S E	10 min ± S E	1 hr ± S E	2 hr ± S E	6 hr ± S E
C O	C	27? ± 0.36	2.68 ± 0?9	1.95 ± 0 18	1 66 ± 0 19	2.06 ± 0.3?
	TNG	2.62 ± 0 16	2.71 ± 0 17	2.1 ± 0 15	1 92 ± 0.30	2.06 ± 0.20
H R.	C	165.3 ± 8 17	172 2 ± 8 8	168 8 ± 3 7	173 ± 6 1	1?9.3 ± 7 4
	TNG	133 8 ± 6 4	1?4 3 ± 10 0	154 1 ± 9 9	149 0 ± 10 9	175 6 ± ??3
S.V	C	17 8 ± 1 68	16 8 ± 2 48	12 4 ± 1 03	10 2 ± 0 6?	11.8 ± 1.39
	TNG	19 2 ± 0 98	17 7 ± 1 06	13 9 ± 0 82	13 4 ± 1.55	12.3 ± 0 94
LVW	C	5 7 ± 0 9?	5 5 ± 0 92	3.5 ± 0 28	2.9 ± 0 97	3.7 ± 0 73
	TNG	4 8 ± 0 44	4 9 ± 0 43	3 4 ± 0 47	3.17 ± 0 ?0	3.13 ± 0 31
TSR	C	54 8 ± 4 5	53 9 ± 3.8	62 4 ± 4 0	80 7 ± 4 1	64 9 ± 9 0
	TNG	53.3 ± 4.2	50 4 ± 3.76	5?.9 ± 4 5	66 6 ± 8 9	60 4 ± 7.3
TPR	C	3 1 ± 0.9?	2.9 ± 0 50	3.8 ± 0 67	4 0 ± 0 84	4 4 ± 1.33
	TNG	4 1 ± 0 6?	3 5 ± 0 69	4.5 ± 0 89	4 3 ± 1 06	6 1? ± 1 02

TNG = Nitroglycerin (0.2 mg sublingual) C O = cardiac output in L/min H R = heart rate in beats/min S V = stroke volume in ml/stroke LVW = left ventricle work in Kgm M min TSR = total systemic resistance in Wood units TPR = total pulmonary resistance in Wood units.
†Represents baseline values at which time no TNG was administered in either group

with the control animals Data were analyzed by group comparison for calculation of t Differences between values with $P < 0.05$ were considered statistically significant

Results

The mortality rate following coronary artery embolization in the control group was 1 out of 7 animals which is similar to the 12 5 per cent (5 out of 40) mortality rate observed in previous control groups using the techniques described here Of the ten animals in the TNG treated group two died following coronary occlusion This mortality rate is not significantly different from the controls

Three minutes of ECG records taken during the time of pressure measurements were examined for arrhythmias Animals with an ECG irregularity during this period were classified as being arrhythmic In the TNG treated group 4 out of 9 animals exhibited arrhythmias one hour after embolization 6 out of 9 at two hours and 7 out of 8 at six hours after embolization Of the six control animals arrhythmias were recorded in 4 animals at one hour after embolization in 2 animals after two hours and in 4 animals after six hours of occlusion There is no statistically significant difference in the number of arrhythmias in the two groups of animals

When the hemodynamic parameters were measured five to ten minutes after administering TNG (0 2 mg sublingual) no significant differences were observed between the control and experimental groups As shown in Fig 1 the mean pressures in the TNG treated group were lower than in the control group although the only parameter which was significantly different was the six hour left atrial pressure

The changes in cardiac output stroke volume, heart rate, and left ventricle work after coronary occlusion are shown in Table I The slight differences between the control and TNG treated groups are not statistically significant The pulmonary and systemic vascular resistance increases following coronary occlusion are also shown in Table I The increase is greater in the control group however, the differences are not statistically significant

Samples of aortic blood pressure records are shown in Fig 2. The records indicate that aortic pressure decreases after TNG treatment with the maximum decrease occurring between two and three minutes after TNG treatment By five minutes after treatment the pressures are nearly returned to the pretreatment level

The results of the effect of TNG treatment on blood biochemical parameters before and after coronary artery embolization are shown in Table II Coronary sinus values are listed however arterial blood samples were also analyzed No statistically significant differences between the control and TNG treated animals were observed before or after coronary artery occlusion.

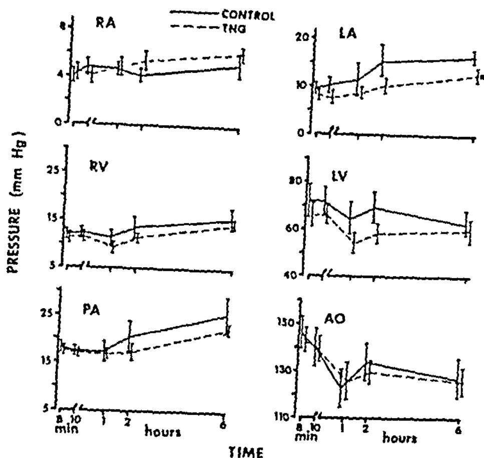


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output and stroke volume suggest no direct myocardial effect of TNG The decreased left atrial pressure observed in the TNG treated animals is consistent with previous reports [?] and is best explained by a decreased venous tone [19] This reduced atrial pressure as well as the reduced systemic resistance and pressures in the treated animals supports the hypothesis that the beneficial effects of TNG are due to a reduced preload and afterload which decreases myocardial oxygen requirement [?, ?, ?]

Most of the results reported here suggest that TNG has no significant cardiovascular effect This ineffectiveness contradicts some previous reports but the differences can be explained on the basis that dosage route of administration and analysis time are different from those used by other investigators The literature contains numerous contradictions in descriptions of the effect of nitroglycerin Some of these differences are due to differences in the time of analysis Even though some investigators report the maximum effect of TNG occurs between five and ten minutes and persists for 30 minutes [?] most investigators analyzed for an effect of TNG within five minutes The results reported here indicate analysis occurring more than five minutes after TNG administration will not show any significant effect Investigators looking for persistent hemodynamic effects of TNG used intravenous infusion [?] The TNG dose used in this study was also less than that used by other investigators who report significant hemodynamic effects for a slightly longer duration than three minutes [?, ?, ?] The dosage of 0 2 mg was selected because it was thought to be more equivalent to the clinical dose than that used by other investigators

In summary the results of the present investigation indicate that TNG is not detrimental to organisms with acute coronary occlusion and that the effect of TNG is transient and of a short duration

Summary

The effect of sublingual (0 2 mg) nitroglycerin (TNG) was studied in anesthetized dogs before and after coronary occlusion Coronary artery occlusion was accomplished by embolization of the circumflex branch of the left coronary artery TNG was administered before embolization and again at one minute one two and six hours after embolization TNG treatment did not significantly increase the number of arrhythmias or deaths compared to untreated animals with coronary occlusion Hemodynamic and blood biochemical parameters were measured 5 to 15 minutes after TNG treatment At this time of measurement blood pressures (AO LV LA PA RV RA) cardiac output pulmonary and systemic resistances and left ventricle work were not significantly different in the TNG treated group compared to the animals with coronary occlusion but no TNG treatment In the first five minutes after TNG administration, aortic pressure is reduced Blood samples withdrawn five minutes after TNG treatment are not significantly different from the untreated animals in Po P_{CO_2} pH glucose lactate pyruvate free fatty acids LDH CPK and SGOT It is concluded that TNG is not detrimental to

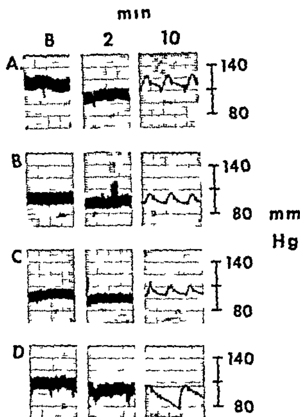


Fig 2 Blood pressure records before (*B*) and 2 and *10* minutes after nitroglycerin treatment (0.2 mg sublingual) *A* 10 minutes after embolization *B* 1 hour after embolization *C* 2 hours after embolization and *D* 6 hours after embolization

Table II Comparison of coronary sinus blood biochemical parameters in TNG treated (N = 10) and control dogs (N = 6) before and after coronary artery occlusion

		Before occlusion		*Following occlusion*		
		Base† ± S E	*10 min* ± S E	*1 hr* ± S E	*2 hr* ± S E	*6 hr* ± S E
Po	C	27.86 ± 1.85	25.63 ± 1.28	26.49 ± 2.13	24.73 ± 1.10	23.96 ± 1.97
mm Hg	TNG	35.56 ± 2.42	29.27 ± 1.83	28.62 ± 1.79	28.4 ± 2.39	23.75 ± 2.49
Pco	C	46.25 ± 3.09	40.53 ± 2.85	37.40 ± 2.28	37.06 ± 1.43	37.07 ± 1.43
mm Hg	TNG	57.50 ± 4.57	50.30 ± 4.74	43.10 ± 3.58	41.38 ± 3.35	36.15 ± 3.11
pH	C	7.325 ± 0.033	7.320 ± 0.107	7.352 ± 0.096	7.396 ± 0.191	7.354 ± 0.113
mm Hg	TNG	7.283 ± 0.0279	7.307 ± 0.0339	7.319 ± 0.1956	7.339 ± 0.0202	7.382 ± 0.033
Glucose	C	113.5 ± 8.8	110.0 ± 9.8	96.7 ± 10.4	85.2 ± 7.0	107.6 ± 6.2
mg %	TNG	117.4 ± 4.3	114.8 ± 4.4	92.7 ± 6.2	92.2 ± 6.7	105.9 ± 5.0
Lactate	C	11.0 ± 3.85	13.1 ± 2.21	23.13 ± 4.54	22.18 ± 4.4	19.46 ± 3.06
mg %	TNG	8.31 ± 1.51	8.86 ± 1.52	14.34 ± 2.76	19.19 ± 3.63	14.74 ± [illegible]
Pyruvate	C	0.09 ± 0.02	0.11 ± 0.012	0.43 ± 0.11	0.45 ± 0.07	0.59 ± 0.04
mg %	TNG	0.18 ± 0.035	0.20 ± 0.086	0.41 ± 0.072	0.62 ± 0.076	0.58 ± 0.06
FFA	C	311.7 ± 51.9	239.5 ± 51.7	445.2 ± 60.2	599.7 ± 123.5	711.5 ± 104.8
mEq/l	TNG	325.3 ± 37.7	314.1 ± 39.6	423.1 ± 76.8	418.7 ± 60.2	518.4 ± 95.1
LDH	C	47.9 ± 5.4	57.0 ± 5.2	77.1 ± 10.0	139.4 ± 33.7	320.7 ± 78.5
IU/ml	TNG	37.8 ± 3.3	49.0 ± 3.5	82.0 ± 11.7	117.1 ± 26.7	270.1 ± 72.4
SGOT	C	27.1 ± 3.4	30.0 ± 1.0	40.4 ± 4.8	77.0 ± 4.8	210.9 ± 35.0
IU/ml	TNG	29.5 ± 1.8	31.7 ± 4.9	45.7 ± 9.4	69.4 ± 17.2	200.5 ± 37.9
CPK	C	6.68 ± 0.70	7.12 ± 0.51	9.67 ± 0.47	26.23 ± 5.04	133.5 ± 19.3
IU/ml	TNG	6.06 ± 0.91	6.80 ± 1.01	10.76 ± 1.54	21.0 ± 3.15	99.3 ± 16.7

Indicates significant difference ($P < 0.05$) from corresponding control value
TNG = Nitroglycerin (0.3 mg sublingual) FFA = plasma free fatty acid LDH = serum lactic dehydrogenase activity SGOT = serum glutamic oxaloacetic transaminase activity CPK = serum creatine phosphokinase activity
†Represents baseline values at which time no TNG was administered in either group

Discussion

Nitroglycerin has been used over a century for the relief of pain from angina The question remains whether or not cardiovascular changes which result in relief of anginal pain could be detrimental in the case of acute myocardial infarction One major effect of TNG is the reduction of systemic pressure as is reported here and by others[10, 11, 13, 22] Parker and co workers[23] demonstrated that reduced systemic pressure does relieve angina, however, Redwood, Smith, and Epstein[24] showed that hypotension and the resultant tachycardia following coronary occlusion increased the ischemic area in the myocardium The reduced systemic pressure also decreases the myocardial perfusion pressure which results in underperfusion of the endocardium and hypoxia[25] In experimental preparations where it was observed that TNG administration reduces the size of the ischemic damage following coronary occlusion, preventing hypotension reduced the ischemic damage even further This indicates that TNG may have an action which prevents the deleterious effect of hypotension induced by TNG[13, 26]

The results of the present study indicate that neither mortality nor arrhythmia frequency is increased by TNG treatment even though systemic pressure was reduced These results do not support the suggestion that TNG administration in the case of acute myocardial infarction would be detrimental Hypotension can result in increased arrhythmia frequency, however, failure to observe increased arrhythmia frequency in the presence of slight hypotension with TNG administration possibly results from its action in raising the fibrillation threshold[11]

The mechanism of action of TNG cannot be established on the basis of the results reported here Blood biochemical parameters are not significantly different in the TNG treated animals compared to the controls In both groups the elevated serum SGOT, LDH, and CPK are an indication of myocardial infarction but the differences between groups are not significant These results and the lack of any effect on cardiac

Coronary hemodynamics during reperfusion following acute coronary ligation in dogs

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Recently surgical techniques were developed in human beings to re-establish myocardial blood flow distal to a coronary obstruction The availability of these techniques to patients with acute myocardial infarction has directed several investigators to evaluate various factors potentially capable of limiting the extent of myocardial damage following an acute coronary artery occlusion Although some histologic and histochemical studies have demonstrated that experimental coronary artery reperfusion would reduce myocardial cell death[1-5] other studies indicate that additional irreversible cardiac damage occurs after the re-establishment of coronary blood flow

The purposes of the present study were to elucidate the coronary hemodynamic effects of re-establishing coronary blood flow to a region of the myocardium rendered ischemic by the acute occlusion of a coronary artery and to assess the regional distribution of the myocardial flow during coronary reperfusion

Materials and methods

Adult mongrel dogs of either sex with an average weight of 21 kilograms were anesthetized with sodium pentobarbital (30 mg per kilogram of body weight) and ventilated with room air by a Harvard respirator After the heart had been exposed through a left thoracotomy in the fifth intercostal space the left circumflex (LC) and the left anterior descending (LAD) coronary arteries were isolated 1 to 2 cm from their origins Electromagnetic flow transducers (Micron RC1000) were placed around the LC and LAD and loose ligatures were placed around each artery 1 to 2 cm beyond the flow transducer By temporarily constricting these ligatures reactive hyperemic responses to 10 sec and 90 sec occlusions were elicited Following the determination of control reactive hyperemic responses an occlusive ligature was secured around the LAD just distal to the flow transducer causing a large portion of the left ventricular wall to become cyanotic Simultaneous measurements of mean aortic pressure left ventricular end diastolic pressure LC and LAD flows and limb Lead II electrocardiogram were continuously made Systemic arterial blood gases pH and rectal temperature of the animal were monitored and kept within normal physiological limits by adjusting the respirator and using a heating pad

Experimental protocol consisted of a 2 hr period of LAD occlusion followed by a 4 hr period of observation after release of this occlusion Throughout these 6 hours in 20 dogs the reactive hyperemic responses to a 10 sec occlusion of LAD and LC were obtained at 30 min intervals except in the LAD during the 2 hr period when it was occluded In an additional group of 6 animals the reactive hyperemic responses to a 90 sec occlusion of the LAD were also obtained at 30 min intervals during reperfusion To define the minimal resistance of the reperfused bed 90 sec occlusions were used since in preliminary experi

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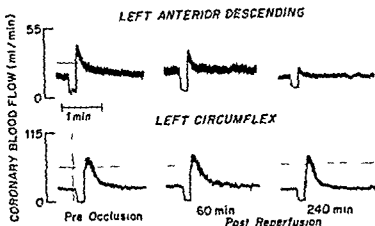


Fig 2 Representative tracings showing reactive hyperemic flow responses to 10 sec occlusions of the left anterior descending (LAD) and left circumflex coronary arteries before LAD occlusion and at 1 and 4 hours during LAD reperfusion

Table I Statistical analysis of transmural distribution of myocardial blood flow in normal and reperfused regions during 5 minutes 2 hours and 4 hours of LAD reperfusion

Blood flow (ml/min/Gm)	Control region			Reperfused region		
	5 min	2 hr	4 h	5 min.	2 hr	4 hr
Epicardial						
Avg ± SE	0.98 ± 0.13	0.92 ± 0.12	0.81 ± 0.10	1.13 ± 0.19	0.59 ± 0.05	0.54 ± 0.13
P	–	–	–	NS	< 0.05	< 0.05
P	–	NS	NS	–	< 0.05	< 0.05
P	NS	–	NS	< 0.05	–	NS
Endocardial						
Avg ± SE	1.07 ± 0.18	1.05 ± 0.24	0.95 ± 0.19	1.17 ± 0.16	0.34 ± 0.03	0.23 ± 0.03
P	–	–	–	NS	< 0.05	< 0.02
P	–	NS	NS	–	0.01	< 0.01
P	NS	–	NS	< 0.01	–	< 0.01
P	NS	NS	NS	NS	< 0.01	< 0.05

P = pr babil ty of statistic l d fference between regions reperfused vs control P = within regions 2 hr or 4 hr vs. 5 min P = within regions, 5 min or 4 hr vs h P = within r gi n endocardial flow vs epic d l flow NS = no significance ($P > 0.05$)

(R_H) in the LAD and LC vascular beds were computed using the peak coronary blood flow following a 10 sec occlusion of the arteries The average values of these resistances in the two vascular beds were plotted in Fig 3 R_H in the LAD vascular bed rose markedly during the period of reperfusion Upon re establishing blood flow in the LAD R_H averaged 34 per cent above the preocclusion control response ($P < 0.05$) at 2 hours it averaged 133 per cent and by 4 hours it reached 153 per cent above control ($P < 0.001$) In the LC vascular bed R_H increased slightly during LAD occlusion but changed little during LAD reperfusion

In a separate group of six animals vascular resistances in the LAD were calculated using the peak reactive hyperemic coronary flow following a 90 sec LAD occlusion Since a coronary occlusion of this duration caused maximal coronary dilation this vascular resistance (R_M) represents the minimal value for LAD coronary resistance The average minimal resistances of the LAD during reperfusion are also plotted in Fig. 3 The minimal resistance in the LAD vascular bed was significantly increased ($P < 0.01$) at 30 minutes of reperfusion and it remained elevated at this level during the period of observation

The response of aortic pressure to LAD occlusion and reperfusion in 20 animals was variable and not statistically different from the preocclu

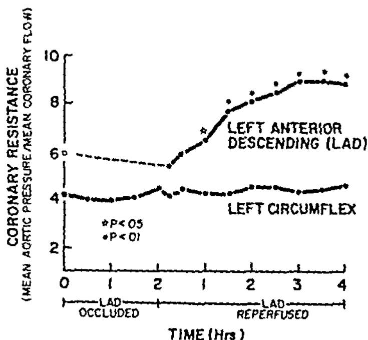


Fig 1 Coronary vascular resistance (in millimeters of mercury per milliliter per minute) in left anterior descending (LAD) and left circumflex coronary arteries during LAD occlusion and reperfusion (n = 20)

ments we observed that occlusions longer than 60 sec did not result in significantly greater dilation of the coronary vasculature Coronary vascular resistances during reactive hyperemia in the LAD and LC vascular beds were computed by dividing the mean aortic pressure (in millimeters of mercury) by the peak reactive hyperemic coronary blood flow (in milliliters per minute) as measured by flowmeter following the release of the 10 sec or 90 sec occlusions of these arteries

Regional distribution of coronary blood flow was determined during the period of reperfusion of the LAD from tissue content of radioactive microspheres of 8 to 10μ diameter administered into the left atrium[9, 10] In 18 of the dogs used in the hyperemic study, one injection of radiomicrospheres was made at the fourth hour of reperfusion In seven of these dogs, two additional measurements of regional blood flow were made by injecting microspheres at 5 minutes and 2 hours of reperfusion These microspheres were labeled with different isotopes ^{141}Ce, ^{46}Sc, and ^{85}Sr Following the last isotope administration, the heart was excised and frozen for sampling Myocardial tissue samples from the free wall of the left ventricle were obtained from both the normal myocardium (control) area supplied by the LC coronary artery, and the reperfused region of the left ventricle, area supplied by the LAD Visually, these samples were divided transmurally into three thirds epicardial, midmyocardial, and endocardial layers The samples were weighed individually and their respective radioactivities were measured by scintillation counting in a three channel gamma detector (Nuclear Chicago 4233) Standard techniques for isotope separation were utilized with the aid of a minicomputer (DEC 8E) Regional blood flow was calculated by relating the radioactivity per gram of myocardial tissue to that of a reference sample of arterial blood collected during each administration of microspheres[11]

Cardiac arrhythmias, mainly ventricular in origin, were usually observed to accompany the occlusion of the LAD and the resumption of the blood flow to the occluded vessels To minimize the frequency of these arrhythmias or prevent their occurrence lidocaine was infused at a rate of 1 mg per minute throughout the experiment This dosage of lidocaine produces no significant systemic hemodynamic effects[12] and if it did influence the coronary vascular system[13] it would be expected to affect both the LAD and LC coronary vascular beds

Results

Coronary resistances Coronary vascular resistances in both the LAD and LC were calculated in 20 dogs and are illustrated in Fig 1 Fifteen minutes after re establishing flow to LAD, the coronary vascular resistance of this bed was practically unchanged (97 per cent of the control) but it rose gradually to 156 per cent of the control at the end of 4 hours of reperfusion Statistically significant ($P < 0.05$) increases in LAD resistances became apparent by 1 hour after establishing flow Coronary resistance in the LC was not changed significantly during LAD occlusion or reperfusion

Representative tracings showing the reactive hyperemic flow responses to a 10 sec occlusion of both the LAD and LC coronary arteries are presented in Fig 2 There the peak hyperemic responses of the LAD after 1 hour and 4 hours of reperfusion can be compared with the preocclusion response of the LAD and that of the LC during the period of LAD reperfusion In the LAD the peak responses became progressively attenuated following reperfusion (upper panel) with little or no change in the LC reactive hyperemic responses (lower panel)

In 20 dogs the reactive hyperemic resistances

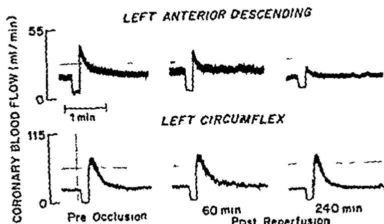


Fig 2 Representative tracings showing reactive hyperemic flow responses to 10 sec occlusions of the left anterior descending (LAD) and left circumflex coronary arteries before LAD occlusion and at 1 and 4 hours during LAD reperfusion

Table 1 Statistical analysis of transmural distribution of myocardial blood flow in normal and reperfused regions during 5 minutes 2 hours and 4 hours of LAD reperfusion

Blood flow (ml./min./Gm.)	*Control region*			*Reperfused region*		
	5 min.	*2 hr*	*4 hr*	*5 min*	*2 hr*	*4 hr*
Epicardial						
Avg ± SE	0.98 ± 0.13	0.92 ± 0.1?	0.81 ± 0.10	1.13 ± 0.19	0.59 ± 0.05	0.54 ± 0.13
P	–	–	–	NS	< 0.05	< 0.05
P	–	NS	NS	–	< 0.05	< 0.05
P	NS	–	NS	< 0.05	–	NS
Endocardial						
Avg ± SE	1.0 ± 0.18	1.05 ± 0.24	0.95 ± 0.19	1.1? ± 0.16	0.34 ± 0.03	0.23 ± 0.03
P	–	–	–	NS	< 0.05	< 0.02
P	–	NS	NS	–	< 0.01	< 0.01
P	NS	–	NS	< 0.01	–	< 0.01
P	NS	NS	NS	NS	< 0.01	< 0.05

P = probability of statistical difference between regions reperfused vs control P = within region 2 hr or 4 hr vs 5 min. P = within regions 5 min or 4 hr vs 2 hr P = within region endocardial flow vs. epicardial flow NS = no significance (P > 0.05)

(R_H) in the LAD and LC vascular beds were computed using the peak coronary blood flow following a 10 sec occlusion of the arteries The average values of these resistances in the two vascular beds were plotted in Fig 3 R_H in the LAD vascular bed rose markedly during the period of reperfusion Upon re establishing blood flow in the LAD R_H averaged 34 per cent above the preocclusion control response ($P < 0.05$) at 2 hours it averaged 133 per cent and by 4 hours it reached 153 per cent above control ($P < 0.001$) In the LC vascular bed R_H increased slightly during LAD occlusion but changed little during LAD reperfusion

In a separate group of six animals vascular resistances in the LAD were calculated using the peak reactive hyperemic coronary flow following a 90 sec LAD occlusion Since a coronary occlusion of this duration caused maximal coronary dilation this vascular resistance (R_M) represents the minimal value for LAD coronary resistance The average minimal resistances of the LAD during reperfusion are also plotted in Fig 3 The minimal resistance in the LAD vascular bed was significantly increased ($P < 0.01$) at 30 minutes of reperfusion and it remained elevated at this level during the period of observation

The response of aortic pressure to LAD occlusion and reperfusion in 20 animals was variable and not statistically different from the preocclu

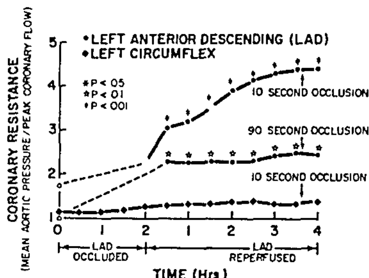


Fig 3 Coronary vascular resistance (in millimeters of mercury per milliliter per minute) during the reactive hyperemias following 10 sec occlusions of the left anterior descending (LAD) and left circumflex coronary arteries and 90 sec occlusions of the LAD

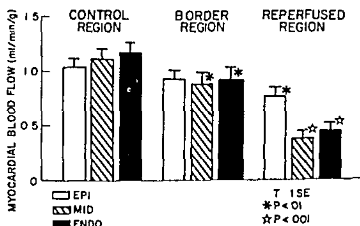


Fig 4 Transmural distribution of myocardial blood flow in the control border and reperfused regions of the left ventricular free wall following 4 hours of left anterior descending coronary artery reperfusion (n = 18)

sion control value (122 ± 5 [S E] mm Hg) after 2 hours (122 ± 3 mm Hg) and 4 hours (116 ± mm Hg) of reperfusion Left ventricular end diastolic pressure in seven dogs was modestly elevated from a control value of 4 ± 0 3 to 8 ± 1 0 and 8 ± 0 8 mm Hg following 2 hours and 4 hours of reperfusion respectively

Distribution of coronary blood flow In seven dogs the distribution of coronary blood flow was determined during LAD reperfusion at 5 minutes 2 hours and 4 hours The average transmural distribution of blood flow in the normal and reperfused left ventricular myocardium are presented in Table I where values for the epicardial and endocardial layers are tabulated

Myocardial blood flow in the control region tended to decrease slightly as the reperfusion progressed, but these changes in blood flows were not statistically significant In contrast the reperfused myocardium showed a significant progressive decline in its blood flow, which was most marked in the endocardial layer While the largest reduction in the myocardial blood flow occurred between 5 minutes and 2 hours of reperfusion there was a further decrease in endocardial flow to the reperfused region during the period between 2 hours and 4 hours of reperfusion

Fig 4 shows the distribution of blood flow to the epicardial midmyocardial, and endocardial layers of the myocardium after 4 hours of reperfusion in 18 animals Blood flows to all layers of the reperfused region were reduced significantly when compared to flows in the corresponding layers of the normal myocardium Epicardial midmyocardial and endocardial blood flows were reduced by 25 ($P < 0\,01$) 65 ($P < 0\,001$), and 61 per cent ($P < 0\,001$) respectively In the border region the area visually outlined between the reperfused and normal myocardium flow was moderately decreased 10 per cent in the epicardial layer and 21 per cent in both the midmyocardial and endocardial layers

Discussion

These experiments demonstrate a progressive hemodynamic deterioration in reperfused canine myocardium Following the re establishment of blood flow to the LAD, the two coronary vascular beds (LAD and LC) behaved differently and independently Coronary vascular resistance in the reperfused region showed a progressive significant increase during the first 3 hours of reperfusion Since this finding is in contrast to the response of the left circumflex coronary vascular bed, it would not likely be neurogenically mediated through an increase in sympathetic autonomic discharge or be the response to lidocaine infusion The increased resistance in the reperfused vasculature could, however, be attributed to local autoregulation in response to a decreased myocardial metabolism or to some structural changes in the vascular bed

The vascular resistance calculated using the peak reactive hyperemic flow following the 90 sec coronary occlusion represents the minimal resistance during reactive hyperemia and reflects the

passive physical component of resistance With this minimal resistance value changes in the coronary vascular resistance resulting from structural changes in the vascular bed could be dissociated from those caused by metabolic or neurogenic factors

During the period of reperfusion of the LAD, minimal resistances were computed only for the reperfused vascular bed Attempts to evaluate minimal resistances in the left circumflex vasculature during LAD reperfusion were largely unsuccessful The additional insult to the left coronary circulation of a 90 sec left circumflex occlusion was not tolerated well and resulted in severe myocardial depression or ventricular fibrillation

The increased passive resistance in the reperfused vascular bed indicates structural changes which appeared shortly after reperfusion was started and continued throughout the period of observation These structural alterations could be attributed to changes in the main coronary vessels or their tributaries or to changes in the adjacent myocardium that tend to increase extravascular pressure and thus increase the resistance to coronary flow The acute development of intracellular and interstitial edema of the reperfused region has been described[1,7] and conceivably this edema is capable of producing an increase in extravascular pressure which limits flow

In addition an increase in coronary vascular resistance could result from the occlusion of the microcirculation by thrombi So as not to preclude this possibility all experiments were conducted without treating the animals with anticoagulants

Coronary vascular reactivity to a 10 sec reactive hyperemia was evaluated in both the reperfused (LAD) and the intact (LC) vascular beds The resistance in the reperfused bed increased steadily during reperfusion while the resistance in the left circumflex bed rose only slightly Since systemic arterial pressure was statistically unchanged throughout the experimental period the marked increase in LAD resistance indicates that the reactive hyperemic flow response to a consistent coronary occlusion period progressively diminished in the reperfused vasculature (see Figs 2 and 3) A reduction of the magnitude of the reactive hyperemic response is indicative of the dysfunction of the reperfused myocardium and most likely reflects the number of viable myocardial cells at a specific time following the re establishment of blood flow to the LAD The progressive decline in reactive hyperemic flow would be consistent with a gradual reduction in the number of the viable cells which in turn would result in a decrease in myocardial oxygen utilization and metabolite production The inability of reperfusion to salvage all of the myocardium traumatized during the acute ischemic period is supported by the observations of Lang and co workers[4] who noted a metabolic deterioration of the reperfused myocardium as indicated by an increased potassium loss and lactate production Another possibility would be that the number of viable myocardial cells does not change but that intrinsic autoregulatory mechanisms become less effective during reperfusion

Thus at this point it cannot be determined if the increase in these resistances are the cause or effect of reduced blood flow in reperfused myocardium The reason for the slight rise in resistance during reactive hyperemia in the intact (LC) vasculature during the period of LAD occlusion and reperfusion is not clear but it indicates the presence of some minor derangement in the intact myocardium as suggested by previous investigations[4]

The use of microspheres as an independent technique for the measurement of myocardial blood flow substantiated the above observation of a marked reduction of blood flow to the reperfused myocardium Four hours after re-establishing flow through the LAD regional flow in the reperfused myocardium was significantly reduced with the endocardial layer showing a greater decrease (61 per cent) Sequential measurements with the microsphere technique showed that flow in the reperfused region was similar to that in normal myocardium at 5 minutes after release of the occlusion but that by 2 hours it was significantly reduced Again and in contrast to the uniform transmural distribution of flow in the normal myocardium a distinctly nonuniform distribution of flow was observed after 2 hours and 4 hours in the reperfused region with flow to the endocardial layer severely compromised During acute coronary occlusion a similar gradient in collateral flow has been observed[15] It would appear therefore that the tendency for myocardial and in particular endo

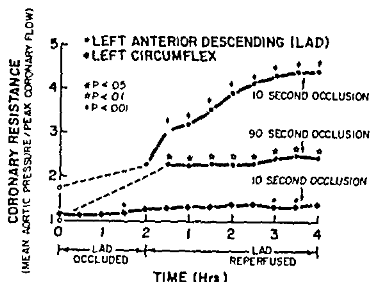


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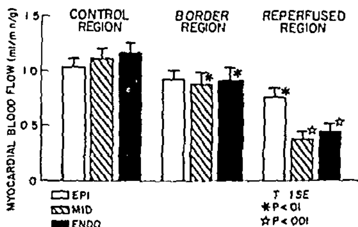


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cardial blood flow to decrease following an acute coronary occlusion is not reversed by coronary reperfusion and this may reflect more extensive damage to that region during the occlusion Furthermore subendocardial flow progressively deteriorated during the 4 hours of LAD reperfusion

The measurements of regional myocardial blood flow with multiple injections of microspheres demonstrate the progressive deterioration of blood flow to the reperfused myocardium and are in agreement with the resistance data showing a progressive increase in resistance or decline in coronary flow to the reperfused tissue The rise in resistance in the LAD during the first 2 hours following the re establishment of blood flow is reflected in the marked decrease in regional blood flow to the reperfused myocardium During the period of reperfusion from 2 to 4 hours when coronary resistance had reached a plateau, further decrease in epicardial blood flow was minimal Endocardial flow however continued to be compromised

Summary

The coronary hemodynamic effects of re establishing blood flow to ischemic myocardium and the regional distribution of myocardial flow during reperfusion were studied in anesthetized open chest dogs A large portion of the left ventricular wall was rendered ischemic by occlusion of the left anterior descending coronary artery for 2 hours During reperfusion of the LAD coronary resistance in the reperfused vasculature increased progressively for the first 3 hours while resistance in the intact LC vasculature was unchanged

Minimal resistances in the reperfused vascular bed calculated from mean aortic pressure and peak coronary reactive hyperemic blood flow following a 90 sec LAD occlusion were elevated significantly during reperfusion The increased minimal resistance values which reflect the passive physical component of resistance indicate structural changes in the reperfused vascular bed which were evident shortly after the initiation of reperfusion and persisted throughout the experimental period Coronary resistances (R_H) in the reperfused (LAD) and intact (LC) vasculatures during the reactive hyperemia following 10 sec coronary occlusions were evaluated During reperfusion, R_H in the reperfused vasculature increased progressively while R_H in the intact bed was unchanged The marked increase in R_H in the LAD indicates that the reactive hyperemic flow response to a consistent period of coronary occlusion progressively diminished and reflects a gradual reduction in the vasodilatory potential of the reperfused coronary circulation

The regional distribution of myocardial blood flow following 5 minutes 2 hours and 4 hours of reperfusion was measured with multiple injections of radioactive microspheres These measurements demonstrated a progressive reduction of blood flow to the reperfused myocardium with no significant change in flow to the control myocardium In contrast to the uniform transmural distribution of flow in the normal myocardium the reperfused region showed a distinctly nonuniform distribution of flow after 2 hours and 4 hours of reperfusion with more severe reduction of flow to the endocardial layer

These studies would suggest that rechannelling blood flow distal to an acute coronary occlusion in human subjects might not in itself be capable of reversing the myocardial injury It is hoped that additional therapeutic measures might be applied to salvage the injured myocardium

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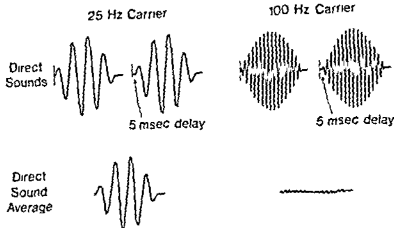


Fig 1 Computer simulation of synchronous averaging of low and high frequency events Cancellation of peaks and valleys of the higher frequency murmur is seen due to time jitter when 5 msec delays occur with respect to the R wave trigger (see text)

filling in the spaces and doubling the number of peaks these peaks are then effaced with a smoothing filter In this way the high frequency signal is *transformed* into its own *low frequency envelope* (Fig 3) As such it can be averaged with minimal phase drift and diminution of signal An ECG monitor is used to synchronize the averager The R wave is the reference point and R to R constitutes an interval The sound envelopes of successive intervals are stored and averaged by a digital processor The composite intensity on the vertical scale vs time on the horizontal is displayed on an oscilloscope and recorded with a Polaroid camera

Bowel sounds breath sounds room noises and other random sounds are progressively diminished while cardiac sounds synchronous with the ECG signal are preserved Very loud random noises (e g a cough) may have an intensity many times greater than a given cardiac signal nullifying the effect of such extraneous sounds would consequently require an average of hundreds of intervals To avoid lengthy averages a reject device is therefore incorporated into the system A short average of eight intervals is recorded during suspended or extremely quiet respiration with care taken to minimize other noise Any subsequent cycle is then excluded if it contains a noise pulse that deviates from the average by more than a set limit

Repeat variability studies performed on two to three different days on 10 patients revealed excellent stability of the recorded sound envelope the configuration timing and duration of the sounds and murmurs retaining their characteristics from day to day (Fig 4) Record variability did not appear to account for diagnostic errors (see below)

Technique

The patient rests supine on a bed with the chest exposed ECG leads are attached and the microphone affixed with double sided tape to any desired chest position Any one of the following frequency bands is selected 100 to 160 Hz 160 to 250 Hz 250 to 400 Hz 400 to 640 Hz and 640 Hz and 640 to 1 000 Hz We have studied many combinations of microphone positions frequency band and length of average but for the purpose of systolic murmur analysis in this study a single average of 128 sweeps was recorded in the fourth left intercostal space at 250 to 400 Hz The average study requires 15 minutes of technician time and physician supervision is unnecessary

Patient selection

Eighty patients were studied Each had one of the following diagnoses proved by echocardiography cardiac catheterization and/or surgery atrial septal defect (ASD six cases) ventricular septal defect (VSD 10 cases) valvular aortic stenosis (AS 30 cases) hypertrophic subaortic stenosis (HSS six cases) rheumatic mitral regurgitation (MR 15 cases) and mitral regurgitation with posterior leaflet prolapse (PLP 13 cases) The prolapsing leaflets developed from ruptured chordae tendineae in seven cases and myxomatous leaflet degeneration in six Two patients with

Sound envelope averaging and the differential diagnosis of systolic murmurs

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In the aftermath of the learning explosion caused by open heart surgery, our attentions have turned back to noninvasive methods. Conspicuous for its lack of re-emergence is standard phonocardiography despite improvements in microphones, amplifiers, filters, and displays. The limiting factor is still, as it always has been, poor signal to noise ratio: the sounds produced by cardiac events exist in a milieu of extraneous noises with overlapping frequencies and intensities. Neither spectral analysis[1] nor accelerography have substantially diminished background noise.

The purpose of this report is to introduce a new instrument that combines rectification, demodulation, and synchronous averaging of repetitive signals with more standard phonocardiographic methods. The result is enhanced signal to noise ratio. To demonstrate the practicality, simplicity, and potential clinical value of the instrument, a patient study is included that explores the differential diagnosis of six common forms of pathological systolic murmurs.

Synchronous averaging

If a signal occurs repetitively and has a fixed time relation to some other signal, then the former can be averaged with the use of the latter as a trigger. Use of a trigger to initiate averaging is termed synchronous averaging. If the signal is contaminated by (stationary) noise, the resulting average will be less contaminated: synchronous averaging improves signal to noise ratio. The heart sound and electrocardiographic (ECG) signals are an appropriate signal-trigger pair. When direct heart sounds are averaged, however, slight variations in the timing between the signal and trigger lead to the cancellation phenomenon illustrated in Fig. 1 and 2. Two examples are shown in Fig. 1. In both, the second occurrence of the murmur is delayed with respect to the trigger by 5 msec. For the low frequency murmur in the left panel, the effect of the time jitter is negligible and the murmur morphology is well preserved. For the high frequency murmur in the right panel, due to cancellation of peaks and valleys, the direct sound average is grossly distorted. Hence, only low frequency signals are amenable to synchronous averaging. (Amplitude randomness in the murmur has not been included in these simplified examples; its effect is similar to that of signal-trigger time jitter.)

Instrumentation

This new instrument* records sounds from the chest wall with a standard piezoelectric microphone, amplifies them, and filters them through band pass filters essentially as in standard phonocardiography. The signal is then rectified and demodulated, that is, the negative valleys are folded up onto the positive side of the record

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*The prototype was designed at the Hewlett Packard Corp., Palo Alto, Calif.

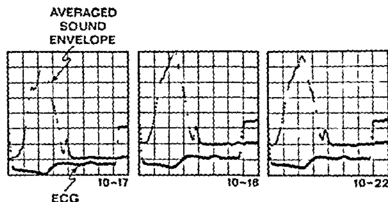


Fig 4 Repeat variability observations made on three separate days from a patient with valvular aortic stenosis. Note that the contours of the systolic murmur and heart sounds are essentially stable from day to day

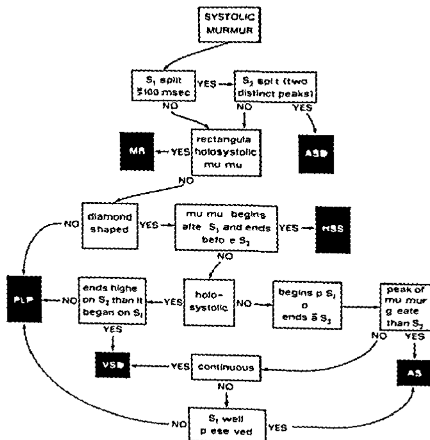


Fig 5 Decision tree The arrows are followed through each consecutive decision box until a diagnosis (the black rectangles) is reached Abbreviations as in text Note that S may be of normal intensity in posterior leaflet prolapse

stenosis produces a crescendo decrescendo contour to the systolic murmur envelope In HSS this murmur follows S and terminates before the onset of S_2 in many instances its onset was unusually rapid with the upstroke of the murmur envelope being steeper than the rate of decrescendo The coexistent pansystolic mitral regurgitant murmur of HSS is not recorded in the left fourth interspace at 250 to 400 Hz In valvular aortic stenosis the sound envelope of the murmur is more typically shaped like an isosceles triangle (diamond shaped) although even in the pres

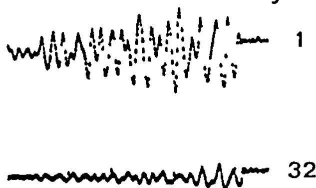


Fig 2 Above Unaveraged standard phonocardiogram showing a pansystolic murmur from a patient with rheumatic mitral regurgitation Below 32 cycles have been averaged with resultant disappearance of the well defined murmur



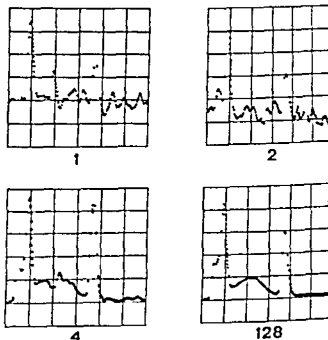


Fig 3 Above A standard phonocardiogram from a patient with valvular aortic stenosis. Note the variability of the systolic murmur contour from beat to beat related to extrinsic noises Below The effect of averaging a rectified and demodulated signal is demonstrated Ambient room and respiratory sounds introduce undesired artifactual noise into the unaveraged recording As averaging takes place however sounds not synchronous with the cardiac events are progressively effaced and a typical sound envelope develops. The reject device was not utilized in this series of recordings for purposes of demonstration

hypertrophic subaortic stenosis and five with posterior leaflet prolapse had documentation of the diagnosis only by echocardiography (see Burgess and associates[1] for detailed differential diagnostic aspects of the various forms of mitral regurgitation and HSS) Patients with functional murmurs, other types of pathological systolic murmurs or combined lesions were excluded from this preliminary study Those with both hypertrophic subaortic stenosis and mitral regurgitation were considered to have only HSS

Blind interpretation

A single Polaroid picture of the averaged phonogram of the first 50 patients recorded at the aforementioned location and frequency was examined Based on the contour duration and relative intensities of systolic murmurs and heart sounds criteria were established in order optimally to segregate the patients into their respective diagnostic groups

The investigators who gathered the data and established the criteria were not involved in subsequent interpretation Five others—two physicians a technician a medical student, and a physicist—examined the same 50 plus 30 additional photographs and segregated them independently Despite the differences in background and knowledge of cardiology their performances were similar each interpreter running an 8 to 12 per cent rate of incorrect diagnoses (see below)

Criteria

The criteria are described in the form of a decision tree (Fig 5) Examples of each characteristic wave form are shown in Fig 6 Atrial septal defect is recognized when the first sound (S_1) splitting exceeds 100 msec and is associated with a well defined split of the second sound (S_2) producing two clear peaks (note that these peaks persist in averages made during normal respiration) The systolic murmur is highly variable and ASD is recognized solely by the characteristic changes in S_1 and S Rheumatic mitral regurgitation produces a typical rectangular envelope and is holosystolic no other category of systolic murmur manifests this rectangular configuration

Outflow obstruction of the left ventricle due to either valvular or hypertrophic subvalvular aortic

Table I Confusion matrix*

Correct diagnosis	Blind diagnosis					
	AS	*ASD*	*HSS*	*MR*	*PLP*	*VSD*
AS	**140**	1	0	3	4	2
ASD	1	**28**	0	0	1	0
HSS	11	0	**14**	1	3	1
MR	2	1	0	**69**	2	1
PLP	3	0	0	1	**59**	2
VSD	1	0	0	1	2	**46**

*The vertical column (see text for abbreviations) represents the correct diagnosis—the patient's actual cardiac disease the diagnoses on the horizontal were those made by the five blind interpreters. Hence the bold face figures represent the number of correct interpretations

Table II Diagnostic accuracy chart

	Total possible correct diagnoses	*Diagnosed by interpreters*	*Correct diagnoses*		*False negative (%)*
			No	%	
AS	150	158	140	93	7
ASD	30	30	28	93	7
HSS	30	14	14	47	53
MR	75	75	69	92	8
PLP	65	71	59	91	9
VSD	50	52	46	92	8
Total	400	400	356		
Mean (%)				89	11

these 225 were correct resulting in an over all accuracy of 90 per cent. Since these were the same 50 photographs from which the criteria were established and therefore likely to yield good results 30 additional ones were then analyzed "prospectively. Of 150 determinations 131 were correct (an accuracy of 87 per cent) Combined the results were 356 right out of 400 (89 per cent) The combined results are presented in the form of a confusion matrix (Table I) and diagnostic accuracy chart (Table II)

Discussion

Looking at *envelopes* rather than directly recorded sound is as old as phonocardiography itself. *Synchronous averaging* is also a time honored and accepted device in engineering physics and medicine. It is the combination of the two techniques that is unique to phonocardiography. The enhanced signal to noise ratio artifact rejection capability and frequency selectivity result in reproducible clearly defined and quantifiable sound contours. The recordings are reproducible from day to day and are little influenced by noises such as respiration borborygmus or room sounds. One weakness of the method results from averaging in the presence of variable heart rates in such cases there is a slight smudging or overlap of cardiac events separated narrowly in time. The duration of a sound therefore appears falsely widened. In the presence of atrial fibrillation the recording is the most unreliable at least beyond early diastole but one could also trigger from the second sound in such instances to minimize this problem

Several limitations of this study deserve mention since the technique is a new one and much of the information is derived from a relatively small data base. (1) Only patients fitting the six disease categories were included for analysis and a number of conditions such as functional murmur multivalvular disease and other forms of congenital heart defect were excluded. Discriminatory accuracy is therefore likely to decline when a wider spectrum of entities is present. (2) The initial portion of the blind analysis was performed on those same records used to define the differentiating criteria. This potential fault was at least partially overcome by the ensuing prospective analysis whereby records not previously considered were interpreted. Diagnostic accuracy remained high in this latter group. (3) No systematic attempt was made to compare this technique with standard phonocardiography although a greater specificity of pattern and more reproducible recording were evident compared with the standard technique. It is not our intention to replace the typical phonocardiogram but rather to combine it with averaged phonography in an attempt to maximize information derived from heart sounds. (4) For analytical simplicity in this study only a single recording taken from the fourth left parasternal space at 250 to 400 Hz was analyzed. Increasing the number of microphone locations and frequency bands should improve differential diagnostic abilities

Most of the differentiating features of the systolic murmurs under discussion have reasonably physiological bases. The increased duration of the first sound seen in atrial septal defect is probably related to the high intensity tricuspid closure sound combined with more typical left sided events. (The widely split averaged second

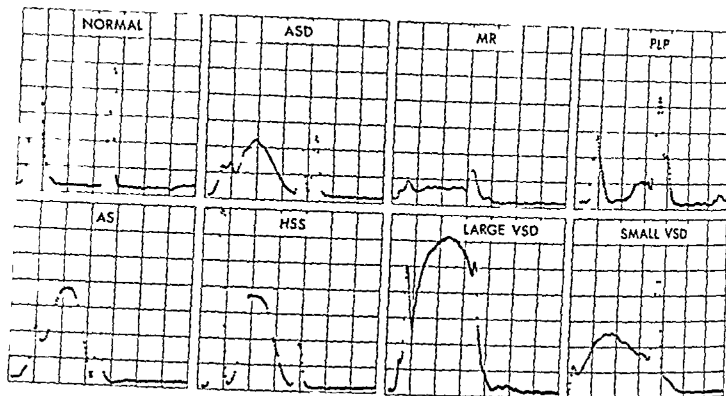


Fig 6 Unretouched prints from Polaroid pictures of the averaged sound envelope A characteristic example of each entity is shown the average being taken of 128 cycles at 250 to 400 Hz Time lines (100 msec) mark the horizontal axis and (uncalibrated) intensity of sound is on the Y axis

ence of severe aortic stenosis the averaged envelope often peaks before midsystole S recorded at the fourth left interspace at 250 to 400 Hz is generally small exhibiting less sound energy than the murmur and S_1 is invariably well preserved Although the murmur of aortic stenosis is generally considered not to be pansys tolic in most instances it is seen on averaging to merge with the base of S_1 and/or S

The contour of the averaged envelope in cases of ventricular septal defect differed from that expected on the basis of standard phonocardiog raphy The murmur was invariably pansystolic merging with S_1 but also showed a late systolic accentuation followed by slight falling off in intensity, such that the end of the murmur blend ed with S at a higher intensity of sound level than with S_1 Three patients had small ventric ular septal defects exhibiting no significant oxygen step up during cardiac catheterization but having positive hydrogen curves recorded in the right ventricle during cardiac catheterization All three of these had 'continuous murmurs' with a spilling of the pansystolic murmur into diastole for a duration of 100 to 150 msec A left ventriculogram in one of these cases demon strated persistence of left to right shunt in early diastole Physical examination revealed the typical pansystolic murmur along the left sternal border with no audible diastolic murmur being present None of the recordings from patients with ventricular septal defects associated with larger shunts showed diastolic continuation of the murmurs

The contour envelopes in patients with poste rior leaflet prolapse were somewhat more variable than in the other groups The murmur envelope was holosystolic often diamond shaped and in other instances exhibited either a decrement or increment in intensity throughout systole S_1 was variable Though generally louder than S_1 in pure rheumatic mitral regurgitation it tended to be normal or soft in some instances where prolapse seemed slight and restricted to the posterior leaflet With greater prolapse and involvement of both leaflets S_1 tended to be increased These subgroups are small and characteristics there fore, tenuous S persisted with normal or increased intensity In contrast to ventricular septal defect the murmur never merged with the second at a location higher than it had with the first

Results

Fifty photographs examined by five observers resulted in 250 diagnostic determinations Of

An inexpensive portable ECG transmitter

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Within the past few years the clinician has witnessed the rapid evolution of the field of electrical monitoring of the heart Continuous electrical monitoring in coronary and intensive care units has been extended to more sophisticated forms of automatic electrical monitoring on the general hospital floor Long term monitoring with a Holter tape recorder has become increasingly popular for outpatient use Telemetry has also been widely applied to transmit ECG information from patients to a remote observer Such applications include radio transmissions from ambulances ambulatory patient radio transmission within the hospital telephone transmission of arrhythmias and telephone transmission of information relating to a pacemaker function

Virtually all of the techniques described require bulky or costly equipment limiting widespread application It is the purpose of this paper to demonstrate how modern electronic technology may be used to construct an inexpensive small ECG transmitter which may be used in conjunction with commonly available demodulators and an ECG recorder for long distance transmission of ECG information over the telephone In addition the varying tone of the device may serve as a bedside indicator of ECG activity

ECG transmitter

The transmitter converts the ECG signal into an audio tone (Fig 1) It is made up of three sections an amplifier (IC 1) a voltage control oscillator (IC 2) and an audio output transformer and speaker (Fig 2)

Conventional monitor adhesive electrodes are placed on the chest wall in the vicinity of the heart The electrodes are generally kept close to each other since large DC skin potential differences may interfere with the operation of the oscillator The electrodes feed an operational amplifier (IC 1) which has a high input impedance

The ECG signal is amplified and sent through a large capacitor to a voltage controlled oscillator (IC 2)

The voltage-control oscillator is an integrated circuit which develops an audio tone suitable for transmission over telephone lines The frequency varies with the amplitude of the output of the operational amplifier integrated circuit

A coupling condensor and audio output transformer carry the frequency modulated signal to a small speaker which is held in close proximity to the telephone mouthpiece for transmission of the tone to a demodulator ECG recorder

Table I Components of the ECG transmitter

R R	500 kohms
R R	44 Mohms
R	1 8 Mohms
R	100 kohms pot
R	1.5 kohms
R R	10 k ohms
C	0 02 μfd
C	200 μfd
C	0 001 μfd
C	47 μfd
T	*miniature audio output transformer*
	?00 Ohm *primary*
	8 Ohm secondary
S	8 Ohm miniature speaker
IC and socket	μA 7?6 Fairchild
IC and socket	NE 566 Signetics
Batteries	2–1 ½ Volt AA cells
	1–9 Volt transistor battery
Battery holders and connectors	
Slide switches	?–SPDT
Electrodes electrode wires wire case and circuit board *All resistors are ¼ watt*	

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sound requires no elaboration) In rheumatic mitral regurgitation the orifice size in systole remains relatively constant and the murmur manifests a nonvarying intensity that appears rectangular in shape By way of contrast a prolapsing mitral valve leaflet produces a change in the regurgitant orifice size during systole, and the extreme pressure elevation within the left atrium may change the left ventricular-left atrial gradient Furthermore, since prolapse is caused by any combination of chordal stretch, leaflet prolapse, or redundant leaflet the resultant patterns would be expected to be multiple and variable

The systolic murmur in hypertrophic subaortic stenosis usually appears clearly separated from both first and second sounds—even during averaging which as mentioned, tends to smudge neighboring events due to slight variations in heart rate This separation can be explained by the fact that left ventricular ejection begins well before the anterior mitral leaflet is pulled toward the ventricular septum, so that the obstruction and murmur are thereby delayed Similarly, it has been shown by both echocardiography and angiography that the anterior leaflet moves away from the ventricular septum in later systole, thus diminishing the gradient and allowing a falling off of the systolic murmur before aortic valve closure has taken place The explanation for the late systolic crescendo followed by slight decrescendo in ventricular septal defect murmurs is not apparent although the recording of inaudible early diastolic continuation of the murmur can reasonably be attributed to a persistent gradient from left to right ventricle during early diastole

We believe this technique provides a useful noninvasive means of enhancing differential diagnostic accuracy in various types of heart disease The technique is quickly and easily performed by a technician and provides reproducible and accurate characterization of the cardiac sounds Average phonography lends itself well to computer analytical techniques and may be additionally valuable as a teaching tool enabling the student to gain a 'feel" for timing frequency, and duration of the various audible events

Summary

Phonocardiography previously has been limited in scope because the attained suboptimal signal to noise ratio has interfered with the sensitivity and clarity of recordings A new system is described that reduces this problem by utilizing demodulation and synchronous averaging of the envelope of cardiac sounds A limited survey of the differential diagnostic capabilities of this technique is presented for 80 patients having one of six common forms of pathological systolic murmurs and an 89 per cent diagnostic accuracy is demonstrated This system promises to be a valuable noninvasive adjunct in cardiologic diagnosis research and education

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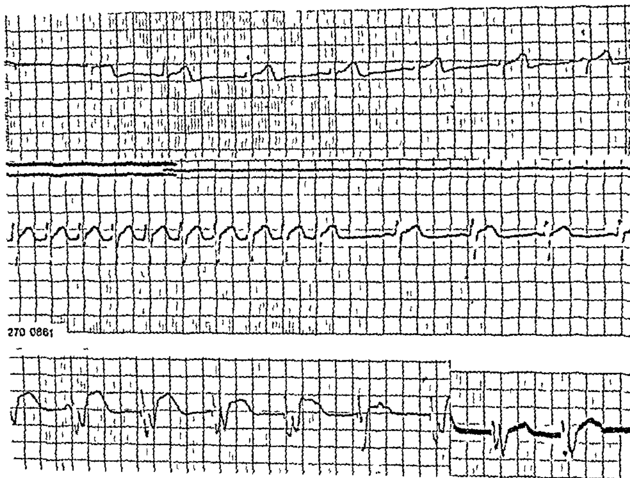


Fig 3 Examples of ECG transmissions from the portable telephone transmitter Top strip is a transmission from New York to San Francisco Middle strip shows the conversion of a paroxysmal atrial tachycardia to sinus rhythm with a Valsalva maneuver Bottom strip shows a demand pacemaker transmission (left) and the subsequent direct recording with a conventional ECG recorder at the bedside for comparison (right)

low cost IC's (approximately $4 50 each) and a few miscellaneous electronic components (Table I) are used in this device

The small number of components involved make it possible for individuals with minimal experience in electronics to construct the transmitter The integrated circuits used in this device are physically small as well as inexpensive and equivalent to many electronic components For example the operational amplifier in the transmitter is 0 370 inch in diameter and 0 185 inch high It contains 24 transistors eight resistors and a capacitor The total cost of the transmitter is less than $20 00

Many hospitals are already equipped with demodulators for converting ECG signals transmitted from various remote sources such as ambulances In such instances the small portable transmitter described may be tuned (R,C) to the frequency of the demodulator and can be incorporated in the existing system In the examples shown (Fig 3) an Electrobiometrics Demodulator[8] was used and the transmitter R C, values did not need to be changed The frequency response of the entire system (transmitter to ECG strip recorder) was 0 5 to 40 Hertz

Widespread use of telephone transmission of ECG signals can be of considerable assistance to the practicing physician (Fig 3) Patients suspected of having various arrhythmias or syncopal problems may have a signal transmitted at a time of distress Likewise pacemakers with potential problems may be analyzed via the telephone as the time for replacement nears It is also possible

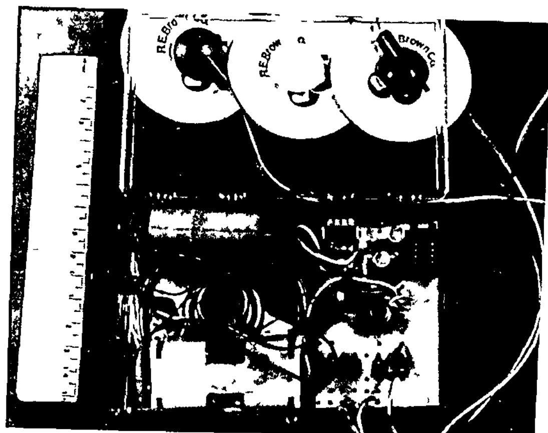


Fig 1 The components of the ECG transmitter are contained within a small plastic box

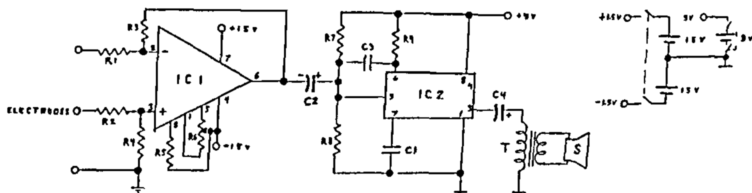


Fig 2 Schematic diagram of the ECG transmitter

The audio tone generated by the transmitter provides the clinician with some information *about the heart beat at the bedside While there is* no substitute for palpation of the pulse the device leaves the physician s hands free for procedures e g , carotid sinus massage In addition the difference in sound of wide QRS complexes such as due *to ventricular premature beats as compared to* the normal duration QRS complex, may be easily detected by the ear Thus in practice the device has some value for use at the bedside as well as for transmission of the signal over the telephone Subsequent voice communication with an interpreter after sending the signal over the telephone provides the sender with information on the transmission

Discussion

Several years ago a multitude of individual components would have been required to construct an ECG transmitter These numerous *components added to the size and cost of the total* unit In the mid sixties the electronics industry developed integrated assemblies of components which were combined to form complete circuits, called integrated circuits The integrated circuit or IC , may be very small and may contain hundreds of separate electronic components Two

Case reports

Oral nitroglycerin as a prophylactic antianginal drug
Clinical physiologic, and statistical evidence of efficacy based on a three-phase experimental design

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Harvey J Berger M D
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Although sublingual nitroglycerin has been the mainstay of therapy of angina pectoris since 1879 there has been considerable controversy concerning the efficacy of oral nitroglycerin The major shortcomings of sublingual nitroglycerin have been its short duration of action and its instability Thus it would be useful to have available an agent which would prevent anginal attacks and myocardial ischemia and yet be taken in separated oral doses throughout the day on a chronic basis As suggested by Krantz[1] a logical approach would be the use of the drug of choice nitroglycerin made long acting and stable by a pharmaceutical process so as to permit a slow and uniform release of nitroglycerin in the gastrointestinal tract

There have been limited well-controlled clinical investigations showing that nitroglycerin administered orally in sustained action form is an effective antianginal drug[2-5] The effectiveness of the oral nitrates has been questioned on grounds of lack of adequate gastrointestinal absorption[6-8] and such rapid hepatic breakdown from the portal circulation that effective circulating blood levels are not achieved[9] However the gastrointestinal absorption of oral sustained release nitroglycerin and prolonged physiologic actions for up to 8 to 10 hours have been documented in recent studies

An experimental design suitable for accurate evaluation of the efficacy of a therapeutic agent in the prophylaxis of angina pectoris has been difficult to develop because there has been little consensus on which anginal characteristics symptoms or findings should be measured[20,21] To study the prophylactic value of oral nitroglycerin a protocol was utilized which included three different approaches (I) the diary method in which anginal symptoms were recorded by patients during daily activities (II) continuous dynamic electrocardiographic (DCG) monitoring of ST segment shifts for 8 to 10 hours during daily routine and (III) standardized multistage treadmill exercise tests to determine the onset and duration of exercise induced anginal pain and the rate pressure product for production of angina The procedures were designed to provide both objective and subjective analyses during extended periods of time of up to 6 months of therapy and take into account the natural life style of the patient Thus the purpose of this study was to evaluate the efficacy of oral nitroglycerin in the long term management and prophylaxis of angina pectoris

Methods

A total of 53 cases were studied The three phases of the investigation were run in succession each phase was completed before the next one was begun The investigation utilized a double blind randomized and cross over design The drug evaluated was a specific controlled release nitroglycerin tablet (2 6 mg)* administered orally three times daily (one tablet before breakfast before dinner and before bed)

Criteria common to all three methods All

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*Nitrong tablets, Wharton Laboratories Inc Div U S Ethicals Inc, Long Island City N Y 11101

to record with tone from the transmitter with a small casette tape recorder for subsequent replay

Summary

A small easy to construct, pocket sized ECG telephone transmitter utilizing few components and costing less than $20 00 is described The tone produced varies with the ECG signal and may be transmitted over the telephone system to a demodulator and ECG recorder for permanent records and interpretation, as well as serving as an indicator of the ECG signal at the bedside This simple device provides useful information on patients with various clinical problems

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tablets used in response to these attacks Supplies of medications were checked by counting remaining tablets to insure accurate reporting of usage

Patients were instructed to score an attack as moderate when it was of average severity mild attacks were less intense severe attacks were more intense than usual Severity scores were calculated by multiplying the number of attacks by values of 1 2 or 3 for mild moderate and severe attacks respectively Systolic and diastolic blood pressures and heart rate sitting at rest were determined during each visit

Sixteen patients 12 male and 4 female (ages 48 to 91 mean 63) completed this study The mean duration of angina prior to the study was 63 months and the mean number of angina attacks per week was 13

II Continuous DCG monitoring of ST segment shifts Patients with left ventricular strain left bundle branch block hypokalemia and those using quinidine or cardiac glycosides were excluded

Using the Holter dynamic electrocardiograph * a Lead CR ECG (bipolar lead from the right clavicle at right midclavicular line to the fifth chest position) was monitored for a period of 10 to 12 hours The light weight recorder, carried comfortably in a leather case with a shoulder strap allowed the patient to undertake usual daily activities [26]

Upon admission to the study at an initial prestudy visit two additional appointments were scheduled for each patient The periods between the initial visit and the first revisit as well as between the two revisits were 6 to 10 days (usually 10 days) Patients were on drug and placebo for the same number of days there was variation of from 6 to 10 days in the duration of therapy because of difficulties in scheduling some patients at exact 10 day intervals DCG recordings were made on the last day of each treatment period Prior to the study pairs of coded bottles (one drug and one placebo) were prepared Each pair was assigned a number based on a table of random numbers [5] The first patient was given pair No 1 subsequent patients received medications in consecutive order At the initial visit patients were given the first bottle and at the second visit the second bottle Neither the physician nor the patient knew the sequence of administration

Patients were instructed to take their medications as usual on the day of testing but they were told to refrain from using sublingual nitroglycerin During recording days patients kept a detailed diary of their activities so that the DCG record could be examined at comparable levels of physical activity during periods of therapy with drug and placebo

The DCG tapes were reviewed at 60 times the recording speed with the use of an electrocardio scanner † Prints of the wave form were made at times corresponding to recorded activities In order to group similar activities in the analysis seven exertional levels were developed ranging from the least strenuous (sleeping) to the most severe (heavy exercise) The specific activities included in each exertional level were derived solely from the diaries of the patients and were given arbitrary numbers which were related approximately to the relative amount of physical activity performed as follows *Level 1* sleeping *Level 2* lying down *Level 3* sitting watching television reading casual card playing personal care *Level 4* dressing undressing preparing for bed standing working at desk *Level 5* walking driving doing housework preparing meals *Level 6* eating drinking sitting at meals *Level 7* walking stairs exercising performing heavy manual labor walking hills

The times and corresponding activities noted in the patient s diaries were listed separately for the two periods of therapy without the DCG tracings or the patient s clinical status Clock hours were converted to time on a 24 hour international scale The sequence of activities on the day of DCG recording during administration of drug was left unchanged however the activities during therapy with placebo were rearranged in order to match each of the activities during drug with the identical activity during placebo at approximately the same time of day Unmatched activities were not included in the analysis The DCG tapes were analyzed independently, without knowledge of the corresponding activities or medications On the basis of five consecutive cardiac beats (excluding ectopic beats) printed from the recordings at the selected times five measurements of the ST segment depression and the heart rate

*Avionics Research Products Corp Los Angeles Calif Mod 1 350E

†Avionics Research Products Corp Los Angeles Calif Mod 1 450

patients were followed by the principal investigator for at least 6 months prior to acceptance into the study. Patients were selected on the basis of the following criteria: at least a 6 month history of clinically stable, well documented angina pectoris, associated with coronary artery disease with regular incidents of characteristic chest pain relieved by sublingual nitroglycerin and electrocardiographic (ECG) findings of old myocardial infarction or ST segment changes consistent with ischemia following exercise, or angiographic evidence of at least one major coronary artery with 75 per cent or greater obstruction. All subjects were ambulatory outpatients and led moderately active lives; none had experienced a myocardial infarction within 6 months preceding entry into the study.

Patients with sudden fluctuations in severity and frequency of anginal attacks, or chest pain due to noncardiac conditions such as diaphragmatic hernia, esophagitis, peptic ulcer, cervical arthritis or gastrointestinal disease were excluded. Patients with significant psychological problems or with complicating forms of cardiac disease such as overt congestive failure, severe valvular disorders, uncontrolled hypertension, or preinfarction angina were also excluded. Patients who had undergone any form of cardiac surgery or those with a history of prophylactic sublingual nitroglycerin usage were similarly eliminated.

Placebos were identical in shape, color, size, taste and scoring to the active drug. All tablets including sublingual nitroglycerin (0.4 mg.) were packed in amber glass bottles with metal screw caps, minimal cotton filling and airtight inner seals to assure uniformity of the medications.

Constant dietary and smoking habits were maintained at all times. No changes in concomitant medications were allowed unless absolutely critical to the patient's well being. The effects of changes in environment were minimized by the relatively constant mild weather in southern California. The psychological effects of the increased attention provided by a personalized research program were taken into account by the use of a double blind cross over design. No patient was given any antianginal medication, except sublingual nitroglycerin, during the week prior to entering the study.

Informed consent was obtained from all patients prior to the clinical trial. Patients were told that at times during the investigation they would be receiving an active drug and at other times an inactive placebo. Additional instructions were not given to patients when medications were dispensed. Bottles contained a supply of drug or placebo for a 2 week period and were labeled with the dosage and the appropriate codes as detailed specifically in following sections. The codes were prepared and maintained by an independent statistician and were unavailable to the investigators until conclusion of each phase of the study.

I. Diary method with daily recording of anginal symptoms. For admission to this phase of the study, all patients had an unequivocal history of at least five anginal attacks per week based on close physician observation over an extended period of months immediately preceding the study. This "rapport period," during which no antianginal drugs except sublingual nitroglycerin were administered, established a stable baseline and determined that the patients were reliable, cooperative, and accurate in reporting their symptoms.[24]

The study was a 6 month multiple cross over comparison of controlled release nitroglycerin and placebo with sublingual nitroglycerin available as needed for pain, but not for prophylactic use. Before the study all possible sequences of six 4 week periods of drug or placebo over a 24 week term were planned. The only limitations imposed on the sequences were that the maximum periods of consecutive therapy with drug or placebo were three or two 4 week periods, respectively. Prior to the study, medication kits composed of 12 coded bottles were prepared corresponding to the possible sequences. Each kit was assigned a number based on the Rand table of random numbers.[2] The first patient was given medication kit No. 1, subsequent patients received medication kits in consecutive order. At the initial visit during the 6 month study, patients were given bottle No. 1, the remaining bottles were distributed consecutively. Neither the physician nor the patient knew when medications were actually crossed over or what sequences were being used.

During the 6 month study, each patient was seen at intervals of 2 weeks at which time the detailed pocket diary of anginal symptoms for the period was turned in and a new bottle of medication was dispensed. Patients recorded the number and severity of attacks, the precipitating factor for attacks (if any could be implicated), and the number of sublingual nitroglycerin

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Upon admission to the study at an initial pre-study visit two additional appointments were scheduled for each patient The periods between the initial visit and the first revisit as well as between the two revisits were 6 to 10 days (usually 10 days) Patients were on drug and placebo for the same number of days there was variation of from 6 to 10 days in the duration of therapy because of difficulties in scheduling some patients at exact 10 day intervals DCG recordings were made on the last day of each treatment period Prior to the study pairs of coded bottles (one drug and one placebo) were prepared Each pair was assigned a number based on a table of random numbers [3] The first patient was given pair No 1 subsequent patients received medications in consecutive order At the initial visit patients were given the first bottle and at the second visit the second bottle Neither the physician nor the patient knew the sequence of administration

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Table I Representative activity matching record for case No 8 (male 69 years old) used in continuous dynamic ECG monitoring study

Treatment Drug						*Treatment Placebo*						
Activity	*Exertional level*	*Time*	*Mean heart rate (beats/min)*	*ST segment depression (mm)*	*Mean seg ment (mm)*	*Activity*	*Exertional level*	*Time*	*Mean heart rate (beats/min)*	*ST segment depression (mm)*	*Mean seg ment (mm)*	*Difference of means*
Standing	4	[illegible]	71	1 0 1 0 1 0 1 2 1 2	1 09	Standing	4	22 00	79	1 0 2 2 1 5 1 2 1 7	1 5[illegible]	0 44
Driving	5	16 00	69	1 5 1 [illegible] 1 0 1 2 1 0	1 21	Driving	[illegible]	16 00	74	2 2 2 5 2 5 1 7 2 5	[illegible]78	1 04
Driving	[illegible]	16 20	76	1 0 0 2 1 2 1 0 0 2	0 72	Driving	5	16 20	79	2 5 3 7 3 0 2 5 2 2	2 [illegible]8	[illegible]
Driving	5	16 30	7[illegible]	1 0 1 5 1 0 1 0 1 0	1 10	Driving	5	16 30	75	2 0 2 0 2 0 2 0 2 0	2 00	0 90
Driving	5	16 45	75	0 5 1 0 0 2 1 0 1 0	0 74	Driving	5	16 4[illegible]	81	2 0 2 0 2 0 2 0 2 0	2 00	[illegible]
Walking	5	18 00	88	1 5 1 5 1 5 0 7 0 7	1 18	Walking	5	20 04	77	2 0 2 5 3 2 2 0 2 0	[illegible]34	1 16
Walking upstairs	7	18 15	90	1 5 1 2 1 5 1 0 1 0	1 21	Walking upstairs	7	18 00	10[illegible]	3 0 2 0 2 0 3 0 3 7	2 74	1 50
Eating	6	18 4[illegible]	77	0 5 0 2 0 5 0 7 1 0	0 58	Eating	6	19 15	85	2 0 2 2 2 7 2 5 3 0	2 48	1 90
Walking	5	20 04	7[illegible]	1 0 1 0 1 0 0 7 1 0	0 91	Walking	[illegible]	15 50	87	2 0 2 0 2 0 2 0 2 0	2 00	1 06
Sitting reading	[illegible]	20 30	70	1 0 1 0 1 2 1 0 1 0	1 04	Sitting reading	[illegible]	20 30	88	1 2 2 0 2 0 2 2 1 5	1 78	0 [illegible]4
Standing	1	22 00	65	0 7 0 7 1 0 1 0 1 0	0 88	Standing	4	18 15	60	2 0 1 7 1 5 1 7 2 0	1 78	0 90
Sitting	[illegible]	22 48	6[illegible]	1 2 1 0 1 5 1 5 1 0	1 24	Sitting	[illegible]	18 4[illegible]	81	1 7 1 7 1 5 2 0 1 5	1 68	0 44
Mean					0 998						2 115	1 11[illegible]
SE of diff												±0 14[illegible]
t value												76[illegible]
												p<0 01

Five consecutive beats were read at each time noted

were determined ST segment depression was read 0 04 seconds after the J point to ±0 1 mm with a magnifying assembly Heart rate was obtained from the R R interval The DCG tapes and their analyses were then matched to their appropriate activities and times Table I demonstrates the final tabulation obtained by using this technique for a representative case Similar records were prepared for each patient

Fifteen patients, 14 males and one female (ages 45 to 85 mean 64) completed this study The mean duration of angina prior to the study was 133 months and the mean number of angina attacks per week was 13

III Exercise tolerance test All patients included in this study had an abnormal treadmill exercise test showing ST segment changes consistent with myocardial ischemia and anginal pain induced by less than 7 minutes of exercise Before the study, all patients were familiarized with exercising on the treadmill and in the absence of any drugs demonstrated a stable, reproducible level of exercise tolerance minimizing the training effect Patients were instructed not to use sublingual nitroglycerin or to smoke on the day of the test Treatments were allocated to patients as in the DCG study (II)

Exercise testing was performed at least 3 hours after a light meal at the same time of day for drug and placebo, and in a room with relatively constant temperature (23 to 25° C) and humidity (60 per cent) On the day of the first revisit, at least 4 hours after tablet administration the patients were exercised on a treadmill* at a constant 10 degree incline The treadmill was started at 1 7 miles per hour (m p h) and increased progressively in grades to 2 0 2 5 3 0 to a maximum of 4 0 m p h The onset of anginal symptoms (tightness pressure, squeezing or pain in the chest) was used as the exercise endpoint On the day of the second revisit the identical exercise test was repeated and terminated at the same amount of pain During testing, the patient s Lead CR, ECG was monitored by telemetry† Parameters measured were the time of

*MD Electronics of Los Angeles Model C
†Avionics Research Products Corp Los Angeles Calif Model 2900

exercise until onset of anginal pain and the duration of pain following termination of exercise

Duration of angina may be considered an expression of anginal severity and the present exercise protocol consistently elicited anginal pain of up to 6 minutes in duration Thus severity grades of 1 2 and 3 were assigned to anginal durations of 0 to 120 121 to 240 and 241 to 360 seconds respectively The exercise index was derived by combination of time to onset and duration of angina into a single parameter The index was obtained by dividing time to onset of pain (seconds) by the severity grade

Time exercised on the treadmill was converted to the equivalent number of feet walked on level ground at a leisurely pace of 2 m p h Treadmill times at 10 degree incline and specific speeds were related to oxygen consumption according to the general formula of Balke and Ware and in turn to oxygen consumed walking at 2 m p h (9 ml of O per minute per kilogram of body weight) * The number of feet walked was derived from the summation of (miles per hour × minutes on treadmill) corrected for oxygen consumption

In a subgroup composed of the last 14 consecutive patients heart rate and systolic blood pressure were monitored before exercise and at time of angina Heart rates were obtained from the R R interval Blood pressures were measured with a sphygmomanometer by the cuff method Left ventricular ejection time was measured from the carotid artery pulse tracing in this group of patients using a volume pulse recorder

Twenty two patients 17 male and 5 female (ages 46 to 80 mean 63) completed this study The mean duration of angina prior to the study was 92 months and the mean number of angina attacks was 9

Statistical methods The significance of differences between drug and placebo was determined within individual patients by a paired t test Mean differences are expressed ± standard error of the difference Differences between groups were analyzed with Student s t test for independent means

Results

I Twenty five patients were entered into the study 12 completed the full 24 weeks four completed only 12 12 22 and 18 weeks The first two patients moved away from the Los Angeles area the third one lost a 2 week diary card the last experienced a mild acute myocardial infarction with an uneventful recovery (Details on the cases that were dropped from the investigation are included in a separate section following the Results)

The total numbers of weeks on drug and placebo were 180 and 172 respectively The mean week numbers for testing of drug and placebo were 12 3 and 10 7 weeks respectively the mean difference was 1 6 ± 1 30 weeks (p > 0 05) These findings demonstrate that drug and placebo were tested for approximately the same total number of weeks and at approximately the same average time during the over all trial They also show that the randomized design was completely balanced with respect to time and treatment

The mean weekly number of angina attacks severity scores and sublingual nitroglycerin doses for the 16 patients are shown in Fig 1 The difference between placebo and drug responses and the percentage improvement are of clinical and statistical significance (p < 0 001) The total number of attacks severity scores and sublingual nitroglycerin used were 2 834 4 652 and 3 006 during 172 patient weeks on placebo and 1 566 2 464 and 1 539 during 180 patient weeks on drug All patients demonstrated a decrease in anginal symptoms on drug therapy when compared to placebo

In the group of 16 patients controlled release nitroglycerin reduced the frequency and severity of anginal attacks by 47 2 and 49 4 per cent respectively and the number of doses of sublingual nitroglycerin used by 51 1 per cent (Fig 2) The difference between drug and placebo was highly significant for this group of patients (p < 0 001) Eleven of 16 patients (69 per cent) decreased sublingual nitroglycerin usage by over 50 per cent Eight of 16 patients (50 per cent) showed improvements greater than 50 per cent in each of the three parameters

The possible development of tolerance to controlled release nitroglycerin was evaluated by comparing the weekly responses of 10 patients who were on drug therapy for at least 8 consecutive weeks (This was determined after breaking of the double blind randomized code and subsequent analysis) An indication of the development of tolerance to the therapeutic action of a drug

Cardiodyne Vasoanalyzer P I Alt Calif Model P 10

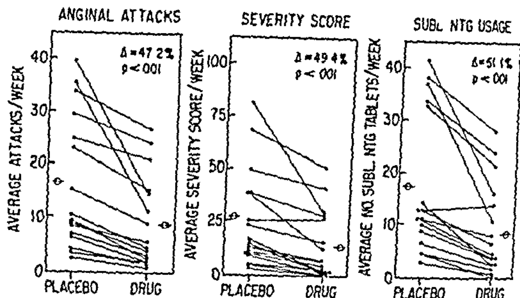


Fig 1 Average attacks severity score and sublingual nitroglycerin (Subl NTG) usage per week compared for each patient on drug and placebo Mean values are given by the circled bars on either side of each panel Drug and placebo are significantly different ($p<0\ 001$) by paired t test in each panel Mean differences (Δ) between drug and placebo are also given in each panel

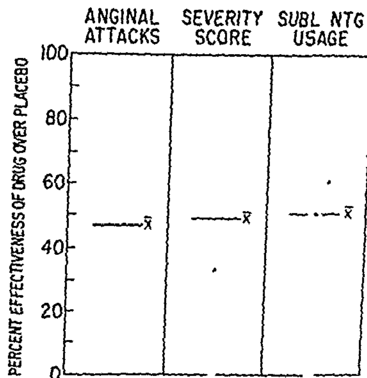


Fig 2 Per cent improvement of drug over placebo (effectiveness) for anginal attacks severity score and sublingual nitroglycerin (NTG) usage Each solid circle represents an individual patient Horizontal bars are means (X̄) for each parameter

would be evident if the response trend showed a steady increase with time beyond a straight line that is an upward concave curvature A quadratic polynomial in time was fitted to each of the 10 sets of data positive linear and quadratic coefficients indicate an upward trend with a concave curvature The coefficients for the linear and quadratic components for each set and for the group were all negative and not significantly different from zero ($p > 0\ 05$) None of the patients showed a positive curvature demonstrating that there was no evidence of therapeutic tolerance to the drug in patients treated for 8 continuous weeks Fig 3 gives the mean weekly sublingual nitroglycerin usage and standard errors for the group of 10 patients and shows a linear response over the 8 week period Similar curves could be drawn for the other two parameters recorded

As shown in Fig 4, drug had no significant effect on systolic and diastolic blood pressures or heart rate in comparison to placebo These data were obtained by averaging the blood pressure and heart rate readings taken at each visit over the entire trial

There were also no significant changes in blood chemistry urinalysis, or hemogram The only side effect which was noted throughout the study was an occasional headache which was reported only while patients were on placebo therapy This was probably due to the increased use of sublingual nitroglycerin during therapy with placebo

II A total of 2 040 separate cardiac cycles for 204 separate activity matched situations were analyzed in 15 patients by a computer technique The results of these matched observations are

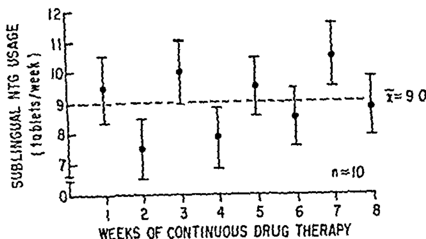


Fig 3 Analysis of tolerance to drug in terms of sublingual nitroglycerin (NTG) usage over an 8 week period in 10 patients Closed circles are mean weekly values vertical bars are standard errors (S E) A quadratic polynomial in time was fitted to each of the 10 sets of data The mean (± S E) linear and quadratic coefficients are − 0 040 ± 0 119 and − 0 019 ± 0 051 respectively The coefficient divided by its S E constitutes a t value Neither coefficient differs significantly from zero (p > 0 05) and the best fitting curve is a straight line with a mean (x̄) of 9 0 None of the individual patients nor the group as a whole showed a positive curvature thus there is no indication of tolerance to drug over the 8 week period

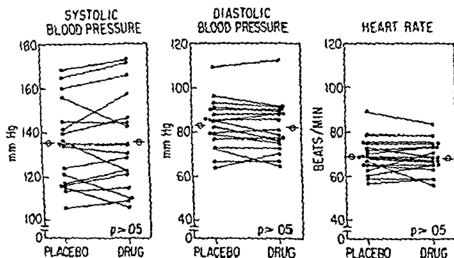


Fig 4 Systolic and diastolic blood pressures and heart rate at rest compared for each patient on drug and placebo Values are means of biweekly recordings over a 24 week period Means are denoted by circled bars on either side of panels There are no significant differences between drug and placebo (p>0 05) by a paired t test

summarized in Fig 5 Drug decreased the ST segment depression from 1 76 mm on placebo to 1 12 mm with a significant difference of 0 64 ± 0 04 mm (p < 0 001) This value is based on a comparison of all ST segment depressions on drug and placebo in individual patients over the 8 to 10 hour monitoring periods Sixty six per cent of the matched activity comparisons demonstrated a reduction in the ST segment shift of greater than 0 5 mm a value considered to be clinically significant in diagnosing myocardial ischemia [7] In the eight patients treated with placebo first the mean difference between drug and placebo in ST segment depression was 0 58 ± 0 05 mm in the seven patients treated with drug first the mean difference was

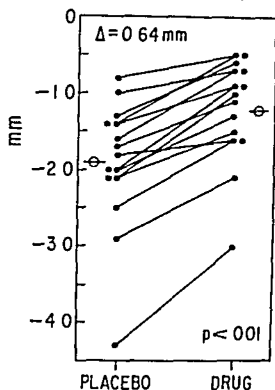


Fig 5 Mean ST segment shift during continuous ECG monitoring over 8 to 10 hour periods compared for each patient on drug and placebo Means are denoted by circled bars on either side of panels Drug and placebo are significantly different by a paired t test (p<0 001) Mean difference (Δ) between drug and placebo is 0 64 mm

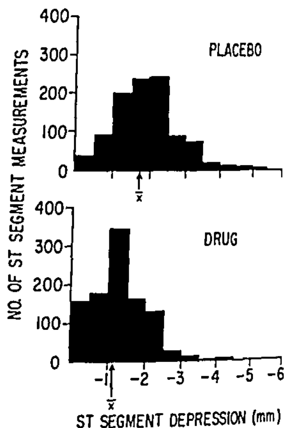


Fig 6 Distribution of 2 040 matched ST segment depressions on drug and placebo for the group of 15 patients during continuous ECG monitoring The number of ST segment readings is shown as a function of ST segment depression There is a leftward shift of the distribution on drug as compared to placebo The means (x̄) for each distribution are noted with vertical arrows

0 74 ± 0 06 mm There was no significant difference between these two groups (p > 0 05)

Fig 6 is a histogram depicting the distribution of increasingly larger ST segment shifts among the 15 patients studied for matched activities at all exertional levels This plot demonstrates that on placebo the largest number of ST segment measurements (246) fell between 2 0 and 2 5 mm however on drug this distribution was shifted significantly to the left (p < 0 001) so that the largest number of measurements (345) fell between 1 0 and 1 5 mm This shift indicates that at a given activity level the same patients showed significantly smaller ST segment depression on drug than on placebo

Fig 7 compares ST segment depression and heart rate with each of the 7 exertional levels The average heart rates varied closely with exertional levels the higher rates being associated with activities that are generally considered more stressful The extremes of ST segment depression noted during exercise (Level 7) were eliminated by therapy with drug This difference between the drug and placebo is highly significant (p < 0 001) Fig 8 shows that the drug administration prevented emergence of ST segment shifts consistent with ischemia and associated with heart rates above 80 beats per minute on therapy with placebo

III Fig 9 shows the time to onset of angina and duration of exercise induced angina The mean time to onset of pain on drug was 214 seconds, whereas on placebo it was 131 seconds representing a significant difference of 83 ± 18 8 seconds (p < 0 001) and a 64 per cent increase in exercise tolerance The duration of angina was reduced from 142 seconds on placebo to 72 seconds on drug a significant decrease of 70 ± 16 1 seconds (p < 0 001) and a 49 per cent improvement In the nine patients treated with placebo first the mean differences between drug and placebo in time to onset of pain and its

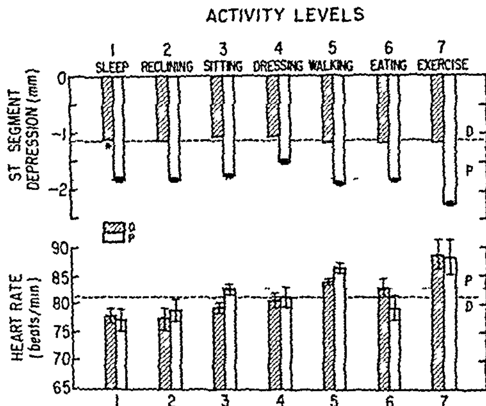


Fig 7 ST segment depression and heart rate as a function of activity levels used in the continuous ECG monitoring study Striped bars represent mean of all values on drug for 15 patients and shaded bars placebo in the same patients. Vertical bars represent standard errors (S E) of the mean Asterisks ( ) denote that S E for striped bars at each activity level in the upper graph are less than ±0 03 and cannot be drawn accurately Over all means for drug (D) and placebo (P) are shown by horizontal dashed and dotted lines, respectively Mean difference of ST segment shift between drug and placebo is statistically significant ($p < 0.001$) but the heart rates are insignificantly different ($p > 0.05$)

duration were 127 ± 39 9 and 60 ± 38 6 seconds respectively In the 13 patients treated with drug *first the mean* differences in these parameters were 53 ± 11 3 and 76 ± 8 4 seconds respectively There were no significant differences in either time to onset of pain or its duration between these two groups ($p > 0.05$) The combined measure of onset and duration the *exercise index was in* creased by drug from 100 to 206 exercise units representing a 106 per cent improvement in over all exercise performance There was a significant correlation between the two components of the exercise index ($r = +0.61$ $p < 0.05$)

The fourth part of Fig 9 presents the treadmill data in terms of number of feet walked The derivation of this parameter is based on the algebraic product of time and work load which gives more weight to increases in walking time at faster rather than slower speeds On placebo patients were able to walk a mean distance of 269 feet whereas on drug their capacity was aug mented to 469 feet an increase of 200 feet This represents an improvement both statistically significant ($p < 0.001$) and *clinically of benefit to* the angina patient suffering from limited exercise capabilities

The product of systolic blood pressure and *heart rate at the* onset of angina has been used as *an indirect measure of myocardial oxygen con* sumption (MVO_2) [33,34] As shown in Fig 10 drug *did not affect* blood pressure heart rate or rate *pressure product* at angina in comparison to placebo However patients on drug reached the rate pressure product for production of angina at 261 seconds instead of at 146 seconds a 79 per *cent delay* The myocardial work load required to *precipitate* angina remained constant regardless of the amount of external work the patient could

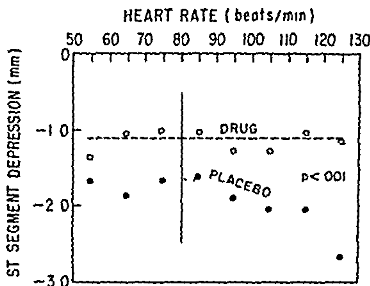


Fig 8 Protective effect of drug (dashed line) on ST segment depression as compared to placebo (dotted line) at higher heart rates The relationship between ST segment and heart rate was analyzed by comparing the slope (increment in ST segment/increment in heart rate) of the drug and placebo trials using a linear least squares method The t value is derived from the remainder sum of squares for the best fit lines Above 80 beats per minute (vertical line) drug and placebo are significantly different ($p < 0\,001$)

undertake Drug did not affect the left ventricular ejection time in comparison to placebo Thus the rate pressure product was not corrected for the ejection time

Patient drop outs Twenty five patients were entered into the diary study (I) but nine of these dropped from the investigation Five patients were discontinued after the second week because they refused to return to the laboratory at 2 week intervals Two patients complained of headaches during the first 2 weeks and thus dropped out Upon breaking the code these two patients were found to have been on placebo One patient complained about the inadequacy of his medication during the first 8 weeks, he was on placebo for the entire period One patient was so unreliable in taking his medications throughout the study that he was not included in analysis

In the DCG (II) there were no dropouts In the exercise study (III) one patient was discontinued because she was unwilling to return to our laboratory within 10 days

Discussion

With the use of a three phase experimental design, oral nitroglycerin in controlled release tablet form was found to be an effective antianginal drug, providing clinically and statistically significant improvement of angina pectoris

Needleman, Lang, and Johnson[9] have demonstrated in the rat that organic nitrates are inactive as vasodepressors when administered by the portal vein They infer that orally administered nitrates are also inactive in man because they pass through the portal circulation However a recent pharmacologic study by Commarato Winbury, and Kaplan[37] directly contradicts their findings Furthermore sustained release nitroglycerin has been shown to be absorbed from the gastrointestinal tract in man and to have a prolonged action of up to 8 to 10 hours[10 19] These facts appear to shed considerable doubt on Needleman s conclusions In vivo physiologic responses in man have also been directly correlated with smooth and uniform in vitro release rate using biomathematical models[11]

Oral nitroglycerin has been found to produce peripheral vasodilatation[11 13 18 19] with decreased arteriolar resistance and increased venous volume[10] These actions reduce ventricular loading and oxygen requirements and decrease resistance to outflow The absence of hypotension following drug administration would suggest compensatory increases in stroke volume and cardiac output, effects which have been documented[16] Such an improvement in myocardial function as a consequence of the reduction of cardiac load would be of particular benefit to angina patients who are unable to adequately increase their cardiac output in response to exercise[38] The increase in cardiac output would partially offset the abnormal left ventricular hemodynamics consistent with angina, yet not affect MVO_2 significantly[39] Additionally, it has been demonstrated that oral sustained release nitroglycerin dilates the coronary arteries and collateral vessels in man[12] and increases the mean vascular capacity of the ischemic left ventricle in the dog[40] Based on the present findings that blood pressure and heart rate are not affected by oral nitroglycerin it seems likely that the actions of this agent on the coronary circulation may be largely responsible for its beneficial antianginal effects A redistribution of coronary blood flow from the epicardium to the endocardium[41 42] or from nonischemic to ischemic areas[43 44] by dilatation of coronary collateral vessels[47 48] could account for such a mechanism

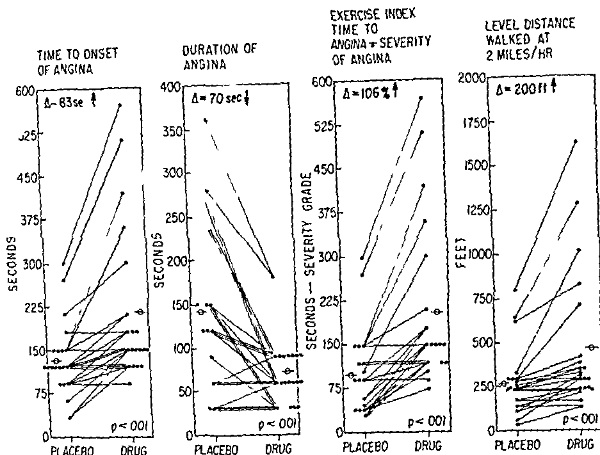


Fig 9 Exercise capacity after placebo and drug therapy in the same patients exercised on a treadmill at 10 degrees. Time to onset and duration of angina expressed in seconds (sec) Level distance walked at 2 m p h. is derived as noted in text Exercise index incorporating both onset and duration is expressed as exercise units (seconds + seventy grade) Mean values are shown by circled bars on either side of each panel. Drug and placebo are significantly different ($p < 0.001$) by a paired t test in each panel Mean differences (Δ) between drug and placebo are indicated in each panel as increase (↑) or decrease (↓)

Although sublingual nitrates commonly cause hypotension and a baroreceptor mediated tachycardia these effects have not been found with the drug under study The absence of these deleterious effects is of particular importance because hypotension may produce an inadequate coronary perfusion [e] and tachycardia may increase MVO_2 [a] electrical instability of the myocardium and the extent of myocardial ischemia [a] The protective action of oral nitroglycerin at higher heart rates was clearly demonstrated in the DCG study (II) as patients on therapy with drug developed significantly smaller ST segment shifts at rates above 80 beats per minute than patients on placebo (Fig 7) Further studies will be needed to elucidate the relative importance of the central and peripheral vascular actions of the nitrates as this issue has not been fully resolved [33] The data presented would suggest that oral controlled release nitroglycerin acts by both mechanisms.

The results in this study may be compared to those of a recent investigation[34] on the sublingual nitrates using a similar exercise protocol and an escalator ergometer technique Forty five minutes after administration sublingual nitroglycerin (0 04 mg) isosorbide dinitrate (5 mg.) and erythritol tetranitrate (10 mg) each increased the time to onset of anginal pain by approximately 45 per cent over placebo In the present study following 6 to 10 days of therapy and at least 4 hours after tablet administration, controlled release nitroglycerin increased exercise tolerance by 64 per cent over placebo This would suggest

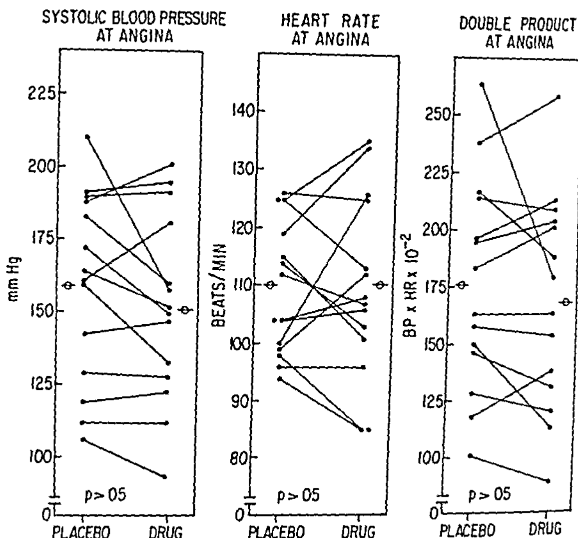


Fig 10 Systolic blood pressure heart rate and calculated rate pressure (double) product at angina for 14 patients on drug compared to placebo Blood pressure was measured by sphygmomanometer and heart rate from ECG tracings There were no significant differences between drug and placebo (p >0 05) by a paired t test Means are shown by circled bars on either side of each panel

that controlled release nitroglycerin is at least as effective as the sublingual nitrates in the doses employed

Tolerance and cross tolerance among the nitrates have been postulated[35 59] but not clearly documented[5 49] With therapeutic doses tolerance has not been demonstrated[60 63] The present findings support the position that nitrate tachyphylaxis does not occur

Sublingual nitroglycerin is unquestionably effective both in the acute relief of anginal chest pain and also in the prophylaxis of pain prior to stress In contrast, there has been lack of consensus regarding the efficacy of oral nitroglycerin and other so called coronary vasodilators with claimed long acting characteristics such as isosorbide dinitrate and pentaerythritol tetranitrate[3 5 49 64 68] It has been postulated that their claimed long acting characteristics, in comparison to sublingual nitroglycerin, may merely be due to inequivalence of dosages[3 69] Aronow[3 4 0] has questioned the efficacy of all drugs in the treatment of angina pectoris Furthermore Redwood and co workers[11] and others[10 12 16] have repeatedly stressed the importance of protocols in the evaluation of antianginal drugs There have been no well controlled investigations that have provided adequate evidence either supporting or opposing the efficacy of oral controlled release nitroglycerin in the management treatment or prophylaxis of angina pectoris The fundamental reason for the inconclusiveness of these studies would seem to be inadequacy of experimental design

A recent review article[10] as well as the guide lines of the NAS/NRC Panel on Cardiovascular Drugs[21] have detailed some of the criteria which need to be considered in study of an antianginal

drug Those variables which might spuriously affect data analysis have been minimized in this study and their suggestions for a well controlled clinical trial have been taken into account The common interpatient variability encountered in angina pectoris as well as the well documented placebo effect of approximately 40 per cent [7,19] were avoided by evaluating responses during therapy with drug and placebo within the same patient To diminish possible bias caused by investigators and patients as well as allocation of treatment periods drug and placebo were compared in a randomized double blind format

Study of a prophylactic antianginal drug should be based on a multiple phase experimental design which takes into account (1) the physiologic basis of angina namely coronary artery disease and myocardial ischemia and (2) the normal life style of the patient Therapeutic agents indicated for long term prophylaxis of angina pectoris should be studied over prolonged periods of time It is for this reason that DCG recording and exercise testing were not undertaken following single dose administration The recording of anginal symptoms by the diary method is a less objective and less reproducible method of analyzing antianginal drugs than either DCG monitoring or exercise testing and thus was carried out over a longer period of time As suggested by Cole Kaye and Griffith [19] antianginal drugs can be evaluated accurately only by using a cross over design and multiple control periods because of the spontaneous fluctuations in the severity or incidence of angina which are encountered Shorter parallel group studies are inadequate in design These requirements for a well controlled study have been incorporated into the three phase experimental design used in this clinical trial With this protocol the efficacy of oral nitroglycerin in the treatment of angina pectoris has been demonstrated

A recent study by Cole and Kaye [9] comparing controlled release nitroglycerin and placebo using the diary method for daily recording of anginal symptoms over a 6 month trial confirmed the findings of the present study They reported reduction in the frequency and severity of anginal attacks by 65 and 66 per cent respectively and the number of sublingual nitroglycerin doses by 63 per cent ($p < 0.001$)

Summary

With the use of a three phase experimental design the efficacy of oral nitroglycerin has been evaluated in a total of 53 patients with documented angina pectoris due to coronary artery disease The study was a double blind randomized and cross-over comparison of controlled release nitroglycerin (2 6 mg tablets administered three times daily) and an indistinguishable placebo Sixteen patients recorded anginal symptoms by the diary method over a 6 month trial of randomly sequenced 1 month periods of drug or placebo In 15 patients ST segments were monitored with a Holter dynamic electrocardiograph for periods of 10 to 12 hours under normal life style and evaluated by matching activities during periods of drug and placebo In 22 patients a multistage treadmill exercise test was conducted to an endpoint of anginal pain The three phases of the investigation were run in succession each phase was completed before the next one was begun

Oral nitroglycerin reduced the incidence and severity of anginal attacks by 47 2 and 49 4 per cent respectively and decreased the number of sublingual nitroglycerin tablets used by 51 1 per cent in comparison to placebo ($p < 0.001$) Eleven of 16 patients (69 per cent) decreased their need for sublingual nitroglycerin by over 50 per cent Based on a polynomial trend analysis over a period of 8 weeks no tolerance to the therapeutic effects of the drug was found With DCG monitoring drug decreased the ST segment depression from 1 76 mm on placebo to 1 12 mm with a significant difference of 0 64 mm ($p < 0.001$) ST segment depression was decreased more than 0 5 mm by drug in comparison to placebo in 10 of 15 patients (66 per cent) Larger depressions of the ST segment noted with placebo at heart rates greater than 80 beats per minute were prevented by administration of the drug During treadmill exercise drug delayed the onset of pain by 83 seconds (64 per cent) over placebo ($p < 0.001$) and decreased the duration of pain by 70 seconds (49 per cent) in comparison to placebo ($p < 0.001$) Drug did not affect heart rate or systolic blood pressure at rest or after exercise as well as rate pressure product for production of angina following exercise ($p > 0.05$) There were no side effects reported caused by the drug The data demonstrate that oral nitroglycerin given as

controlled release tablets was absorbed from the gastrointestinal tract in quantities sufficient to provide statistically significant clinical improvement of angina pectoris

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Probable postcardiotomy syndrome following implantation of a transvenous pacemaker
Report of the first case

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The postcardiotomy syndrome may follow cardiac surgery myocardial infarction and blunt and penetrating trauma to the chest[1] To the knowledge of the authors this syndrome has not been reported as a consequence of implantation of a transvenous pacemaker As perforation of the right ventricle is a complication of placement of a pacemaker wire[2] it is not unexpected that the "postcardiotomy syndrome" should occasionally follow placement of a transvenous pacemaker

The purpose of this report is to describe a patient who developed a probable "postcardiotomy syndrome" following placement of a transvenous pacemaker

Case report

M K, a 72 year old white male was admitted to the Hospital of the Medical College of Pennsylvania for a right inguinal herniorrhaphy The past history was unremarkable except for the presence on electrocardiogram of a left bundle branch block starting six years prior to admission evolving into a right bundle branch block with left anterior hemiblock two years prior to admission This electrocardiographic finding had been stable for the past two years during which time electrocardiograms were obtained at least every three months Two years prior to admission digoxin therapy had been started and continued at a dose of 0 25 mg each day because of presence of five to six atrial and ventricular premature contractions each minute With digoxin these had decreased to about one premature contraction per minute There had never been any signs or symptoms of heart failure (i e dyspnea orthopnea or edema) or episodes of chest pain

On May 3, 1973 a temporary transvenous demand pacemaker was inserted into the right ventricle without incident for prophylactic reasons because of the presence of bifascicular block, although we realize that this indication is questioned by some authors On May 4 the hernia repair was performed and the pacemaker remained in place for 72 hours On May 14 1973 a Cordis permanent demand pacemaker was implanted subcutaneously in the left chest for prophylaxis against complete heart block The patient was discharged from the hospital following an uneventful postoperative course

On about May 21 he resumed normal activity which included walking long distances Several days later he began to note bilateral ankle edema every evening which cleared by morning

On June 6 a chest x ray on a routine visit demonstrated a 1 5 cm increase in the transverse diameter of the heart which had been normal on May 15 1973 (Figs 1 and 2) There was also a small right pleural effusion Electrocardiograms were unchanged and showed normal sinus rhythm The pacemaker was suppressed because the inherent sinus rate exceeded that of the pacemaker A magnet was then placed over the pacemaker causing it to fire in a fixed rate mode The pacemaker was thus found to be pacing well, and its failure to fire during sinus rhythm indicated that it was sensing well

On July 20 the patient returned for a routine pacemaker check. He had been feeling well and working six days a week but had noted malaise for the preceding five days His temperature was noted to be 102 6 F rectally The physical examination was within normal limits except for 2+ pitting edema of both feet Specifically the neck veins were flat the liver was not palpable and the site of implantation of the pacemaker was well healed and nontender

Electrocardiograms showed normal sinus rhythm and were unchanged The pacemaker paced properly on magnetic stimulation. On chest x ray the pacemaker was in proper position and the lung fields were normal but the heart was 1.5 cm larger in transverse diameter than on June 6 (Fig 3) During the next seven days (July 21 through 27) fever continued with a daily rise to 102 to 103 F rectally but the

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Fig 1 Chest x ray taken on May 16 1973 (the day following implantation of the permanent pacemaker) The transverse diameter of the heart is normal



Fig 2 Chest x ray taken on June 6 1973 demonstrating a 1 5 cm increase in the transverse diameter of the heart and a small right pleural effusion

patient felt relatively well Temperatures were recorded four times a day To evaluate the possibility of a pericardial effusion a carbon dioxide study was performed on July 23 and was consistent with a pericardial effusion (Fig 4) The same day the patient had the onset of a nonproductive cough Complete blood count and urinalysis were normal as were several determinations of blood urea nitrogen serum creatinine serum electrolytes CPK SGOT SGPT and serum protein The erythrocyte sedimentation rate was 20 (upper limit of normal 10) Five blood cultures were negative

On July 25 the patient had mild left posterior pleuritic chest pain that lasted for only one day On July 26 a pericardial friction rub was heard for the first time The electrocardiogram was unchanged The chest x ray revealed clear lung



Fig 3 Chest x ray taken July 20 1973 demonstrating a 1 5 cm increase in the transverse diameter of the heart over the x ray of June 6

fields and the heart size was unchanged from July 20 During the next five days (July 28 through Aug 1) the temperature reached only 101° F rectally each day and the cough began to improve From Aug 2 through Aug 14 the rectal temperature continued to reach 100 2 F each day and the pericardial friction rub became louder On Aug 3 the heart had decreased by 1 cm in transverse diameter on x ray The dependent edema in the evening diminished and disappeared

By Aug 24 the patient had become completely afebrile the cough had stopped and heart size had decreased to normal (Fig 5) The pericardial friction rub gradually became much softer it was barely audible on Sept 1 1973 and disappeared by Sept 7 1973

The pacemaker wire remained in proper position on chest x rays taken at least weekly during the febrile illness and the pacemaker paced properly (when stimulated with a magnet) as judged by electrocardiograms taken at least weekly during the illness At no time during the illness did the patient experience anterior chest pain dyspnea or orthopnea and the neck veins were flat on frequent examinations In fact except for the visits to the doctor the patient worked eight hours a day during the entire illness No therapy was given except for continuation of digoxin 0 25 mg each day Cold agglutinins, latex agglutination and serum antibody titers against Coxsackie viruses B1 through 6 and against *Mycoplasma pneumoniae* did not rise during the illness The patient is well with a normal size heart on x ray as of April 1974

Discussion

This 72 year old man had fever documented for 26 days and he probably had fever for at least five days before documentation and for up to 10 days after The only localizing findings on history and physical examination were cough mild pleuritic

pain of short duration and a pericardial friction rub It seems likely from the course that the chest x ray showing enlargement of the heart six weeks prior to documentation of fever represented a pericardial effusion The illness most suggests either viral pericarditis or the postcardiotomy syndrome However the probable presence of a pericardial effusion for six weeks prior to onset of fever would be extremely unusual in viral pericarditis Furthermore viral pericarditis is unusual in elderly patients Although there is no way of proving a diagnosis of postcardiotomy syndrome the patient's clinical course (appearance and resolution without therapy of febrile pericarditis) following insertion of a transvenous pacemaker most suggests this diagnosis It is possible that the edema which appeared nine days after insertion of the permanent pacemaker and 20 days after insertion of the temporary pacemaker was related to pericardial effusion and resultant mild tamponade At the time of appearance it was attributed to the period of inactivity following the hernia repair

Inadvertent perforation of the ventricle has been reported during insertion of transvenous pacemakers However when it occurs it is transient since the pacemaker wire is then pulled back until the position of the tip is correct The physicians performing the procedures in our patient did not recall any difficulty with placement of either the temporary or permanent pacemakers However the possibility of ventricular wall perforation occurring without recognition certainly must be considered in any patient undergoing these procedures The trauma caused by perforation of the ventricle with bleeding into the pericardial sac would be sufficient to account for the subsequent syndrome which is known to follow cardiotomy myocardial infarction and penetrating or blunt trauma to the chest In our patient there was no evidence of a myocardial infarction nor was there blunt trauma to the chest

The postcardiotomy syndrome is presumed to occur from an autoimmune reaction[4] and usually follows trauma to the heart or pericardium It may appear from one week to three months after the event but most often occurs within two to four weeks Fever and pericarditis are the most common manifestations but pneumonia and pleuritis are also reported

It is not known why the postcardiotomy



Fig 4 X ray of the heart following intravenous injection of carbon dioxide on July 23 1973 demonstrating a pericardial effusion



Fig 5 Chest x ray taken on August 24 1973 demonstrating return of the transverse diameter of the heart to normal

syndrome has not been described before in patients receiving transvenous pacemakers Several explanations may be offered The syndrome may be rare because of relatively little myocardial trauma (from perforation) as compared with the extent during cardiac surgery or myocardial infarction Furthermore the syndrome may not be detected in its milder forms Our patient had few symptoms was not even aware of fever and

continued to work during the entire illness Another factor to be considered is that other diagnoses are more likely to be made in patients following pacemaker implantation because the postcardiotomy syndrome has not, to date been reported to follow this procedure

It is hoped that this case report will cause physicians to be alerted to the possibility of this syndrome developing following implantation of pacemakers and thus evoke other reports

Summary

The syndrome of fever and pericarditis is reported following implantation of a transvenous pacemaker in a 72 year old man The pacemaker was placed for prophylactic reasons (i e presence of bifascicular block) The syndrome resolved spontaneously after over four weeks of fever and a pericardial friction rub Perforation of the right ventricle although not recognized in this patient is a complication which occurs with passage of a transvenous pacemaker

There were no other antecedent events to explain the syndrome such as myocardial infarction or trauma to the chest

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Note

Coronary angiographic echocardiographic and electrocardiographic studies on a patient with variant angina due to coronary artery spasm

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Spasm in an angiographically normal coronary artery as an etiology of variant or Prinzmetal s angina has recently been described [1] It is the purpose of this report to provide further evidence in support of this entity This is the first case in which the effect of coronary arterial spasm upon septal motion has been documented echocardio graphically

Case report

A 45 year-old female was admitted to Indiana University Hospital with a one year history of constricting substernal chest pain with radiation to the neck and arms The pain would occur spontaneously and with exertion but at times the patient remained pain free during heavy exertion Nitrogly cerin always afforded prompt relief from the chest pain The patient had no history of hypertension or diabetes mellitus Coronary cineangiographic studies three months previous at another institution were normal.

The admitting physical examination was normal A com plete blood count and urinalysis and all routine blood chem istry tests were normal, as was a serum lipid profile A resting electrocardiogram (ECG) was within normal limits (Fig 1) An electrocardiogram taken the same day during an episode of spontaneous chest pain demonstrated ST elevation with symmetrical peaked T waves in Leads V through V (Fig 2) During a subsequent episode of spontaneous chest pain frequent ventricular premature complexes and short runs of ventricular tachycardia were observed on an ECG monitor

A graded treadmill exercise test was performed according to methods previously described During the study symmetrical peaked T waves slight ST elevation and short runs of ven tricular tachycardia were observed concurrent with the onset of angina (Fig 3) Following recovery from exercise the patient performed rapid repetitive isometric hand grip exercise util izing a hand dynamometer ECG changes similar to those during treadmill exercise occurred simultaneously with the onset of angina (Fig 3)

Echocardiography was performed with a commercial ultra sonoscope (Ekoline 20) utilizing a 0 5 inch diameter 2 25 mHz transducer with a repetition rate of 1 000 pulses per second and focused at 7 5 cm A simultaneous Lead II ECG and the M mode echocardiogram were recorded and displayed on a multichannel strip-chart recorder (Electronics for Medicine) The resting echocardiogram performed according to methods previously described was normal. The transducer was then directed to a position below the mitral valve leaflets so that the ventricular septal and posterior wall endocardial echoes were clearly seen An echocardiogram with transducer held stable was continuously recorded during successive periods of rest isometric hand grip stress and recovery (Fig 4) The stress period consisted of three minutes of sustained hand grip at a force of 6 kg (1/3 of maximum hand grip force for this patient) During stress the patient experienced her usual chest pain and the left septal amplitude (LSa) decreased from the 8 mm measured during the control period to 3 mm There was no change in the left ventricular end-diastolic internal dimen sion (LVIDd) or the posterior endocardial motion (EN) Thirty seconds following the termination of stress LSa had returned to mm

One day following the exercise tests left heart catheteriza tion with selective coronary cineangiography was performed by the Judkins technique Selective opacification of the coronary arteries with Renografin 76 was observed on a Philips 6-inch image intensifier The output was photographed at 64 frames per second on 35 mm Eastman XX negative cine film by an Arriflex camera with a lens focal length of 100 mm Following introduction of the catheter into the left coronary ostium repeated opacifications of the vessel were accom

F m the K n ert Inst tut of Card l gy M rion C u ty G eral Hosp tal, d th Department f Medici Ind an Un rs ty School f Med in I d n polis.

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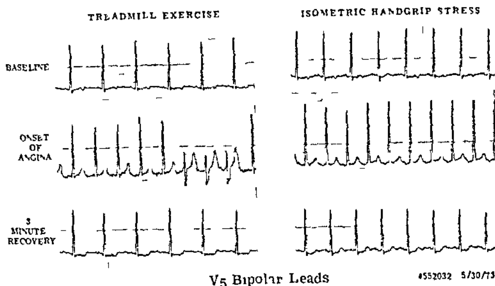


Fig 3 Bipolar Lead V recordings during treadmill exercise and isometric hand grip stress tests During treadmill induced angina slight ST-segment elevation symmetrical peaked T waves and a short run of ventricular *tachycardia occurred.* Similar ST and T wave changes and inverted U waves occurred with angina during isometric hand grip stress

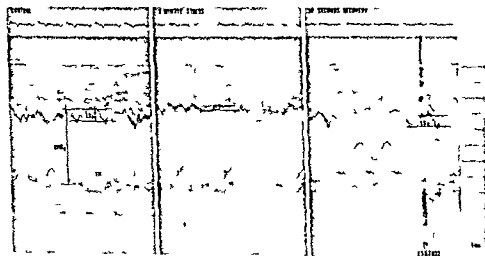


Fig 4 Segments of continuous *echocardiogram* recorded during isometric stress. Normal left septal amplitude (SLa) and posterior endocardial (EN) *motion was present* during the control period Isometric stress precipitated angina and a simultaneous decrease in LSa The *left ventricular* end diastolic interval dim nsion (LVIDd) remained unchanged. During recovery septal motion returned to normal

plished before and during hand grip stress with no further manipulation *of the catheter* tip Two right anterior and two left *anterior* oblique views of the left coronary system with the patient at rest and pain free *were normal.*

Angina was then *precipitated* under the stress of isometric handgrip exercise A selective left coronary injection in the right anterior oblique projection during the episode of angina revealed spasm *of the* left anterior descending artery proximal to the first *septal* perforator (Fig 5) Multiple views of the right coronary artery prior to and during an episode of spontaneous angina were normal.

Discussion

The pathophysiology of episodes of myocardial ischemia in variant angina is thought to be re lated to a significant obstructive lesion of a major coronary artery with or without associated coronary arterial spasm A few cases of variant angina with *angiographically* documented coro nary arterial spasm in otherwise *normal* coronary arteries have been reported Oliva Potts and

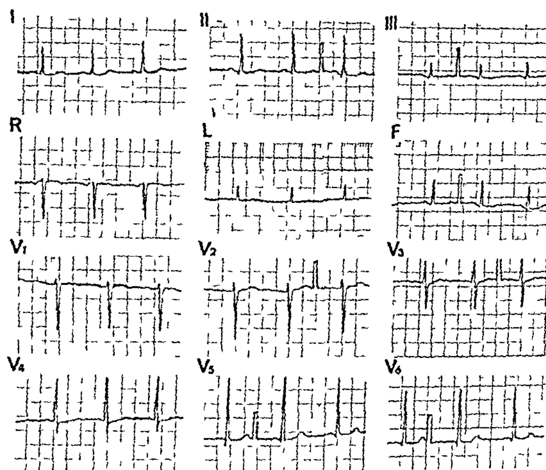


Fig 1 Normal admission ECG

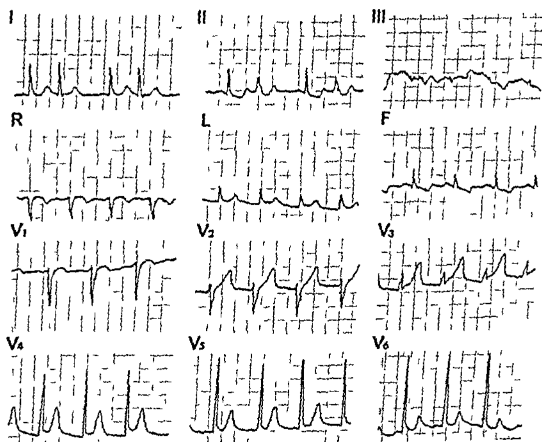


Fig 2 ECG taken during spontaneous episode of angina Note elevation of ST segments and symmetrical peaked T wave in Leads V_2 through V_6 Ventricular bigeminy recorded in Leads I and II

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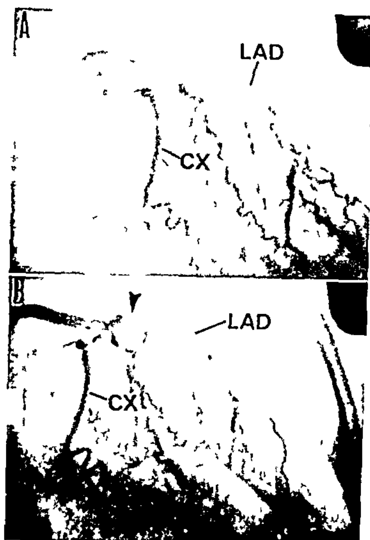


Fig 5 Left coronary arteriogram in right anterior oblique projection *A* Normal left anterior descending (LAD) and circumflex (CX) coronary arteries with patient at rest and pain free *B* Same projection during angina induced by isometric stress Note spasm (arrow) of left anterior descending artery (LAD) proximal to first septal perforator

Pluss[1] reported a single case involving the right coronary artery Chang and co workers reported two patients in whom spasm in a normal right coronary artery was angiographically documented Other reported cases of variant angina with normal coronary arteries lack angiographic proof of spasm [11]

In this case spasm in an otherwise normal left anterior descending artery was angiographically demonstrable following the precipitation of angina with isometric hand grip stress Although catheter induced spasm in this as well as all previously reported cases cannot be completely ruled out [11, 12] we feel this is an unlikely possibility in our case Extreme care was taken to minimize catheter manipulation and the contrast material was not injected into the left coronary artery until the patient s episode of angina had fully developed Furthermore, during previous episodes of both spontaneous and effort induced angina electrocardiographic and echocardiographic evidence of myocardial ischemia in the areas supplied by the left descending artery was demonstrated The ECG during angina demonstrated ST segment elevation and peaking of the T waves in the precordial leads as well as ventricular arrhythmias The echocardiogram displayed normal septal motion with the patient at rest and pain free but during isometric stress induced angina abnormal septal motion was recorded Similar, but stable, abnormalities in septal motion have been described in patients with angiographically demonstrated fixed anterior descending artery lesions [11] The septal motion may be absent, paradoxical, or, as seen in our patient diminished Thus, we feel this patient represents another case of variant angina due to coronary arterial spasms in an otherwise angiographically normal coronary artery

Summary

A 45 year old Caucasian female patient with a clinical history and ECG's conforming to the syndrome of variant angina as characterized by Prinzmetal is presented ECG s recorded during spontaneous pain demonstrated ST segment elevation and symmetrical peaking of the T waves in the lateral precordial leads and short runs of ventricular tachycardia Similar ECG changes were recorded during treadmill exercise and hand grip exercise induced chest pain An echocardiogram recorded during angina induced by hand grip exercise demonstrated progressive flattening of septal motion Multiple views of the coronary system by selective coronary cineangiography were normal with the patient at rest Angina was then induced by hand grip exercise and a repeat right anterior oblique view of the left coronary system revealed marked spasm of the left anterior descending artery proximal to the first septal perforator

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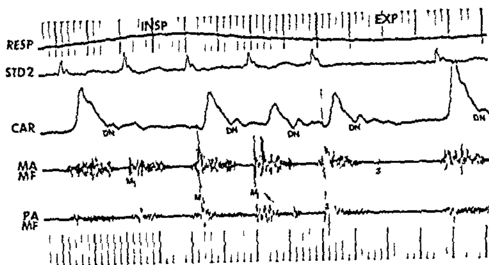


Fig 1 Phonocardiogram recorded during respiration of a 64 year-old man with ruptured chordae tendineae to the posterior leaflet. The crescendo-decrescendo systolic murmur of pure severe mitral regurgitation is shown. The mitral component (M) of the first heart sound varies in intensity After one short diastole a second major left sided component (arrowed) of the first sound is recorded which is caused we believe by asynchronous maximal tension on the two mitral leaflets and their chordae at that time (see text) *CAR* = indirect carotid pulse tracing *DN* = dicrotic notch *MA* = mitral area *PA* = pulmonary area *MF* = medium frequency 3 = third heart sound Time lines = 0 04 sec

A delayed tricuspid component of the first heart sound in Ebstein s anomaly which we postulated [4] was due to billowing of the abnormal tricuspid leaflet has also been called a systolic click [5] The tricuspid origin of that sound has subsequently been confirmed[5, 59] and the term "sail sound" suggested [59] An analogous mechanism is probably responsible for a second major left-sided component of the first sound which we have observed in some patients with ruptured chordae tendineae of the mitral valve (Fig 1) or after surgical insertion of a pericardial patch into the posterior leaflet [60] Since these "double mitral or tricuspid components of the first sound occur in specific conditions and unlike early nonejection clicks have a constant time relationship to atrial and ventricular pressure events [4] we consider that the term nonejection systolic click should not be used to describe them

When a nonejection systolic click is associated with mild mitral regurgitation the systolic murmur and thus the regurgitation are often confined to late systole The term late systolic seems satisfactory to describe this murmur However it must be emphasized that such late systolic murmurs can temporarily move earlier and sometimes become longer with certain hemodynamic changes [3, 27, 30, 32, 5, 1-6]

Underlying etiology In an analysis of 220 patients who presented with the auscultatory features of a late systolic murmur a nonejection click or both [33] a number of conditions were thought to be responsible for the pathology of the mitral valve mechanism (Fig 2) Most of these etiologic factors have been mentioned or confirmed in other reports [3, 18, 21, 23, 26, 61, 7] Conditions which are not represented in Fig 2 but which may result in these auscultatory features arising at the mitral valve include congestive cardiomyopathy [3] subvalvar left ventricular aneurysm [7] myocarditis [7] and atrial myxoma[2, 4] (Fig 3)

Prevalence Contrary to a previously expressed opinion from this laboratory [7] we now realize that nonejection clicks and to a less extent late systolic murmurs are common findings in routine cardiologic practice We have learned as have others [3, 5, 34, 5] that when these auscultatory features are specifically sought an ever increasing number of subjects are found to have them Subsequent to our reported 220 patients [2, 33] we have encountered more than 200 patients in this Clinic the majority of whom were referred because of symptoms or for the elucidation of auscultatory signs or abnormal electrocardiogram (ECG) These numbers do not provide data from which the prevalence of the auscultatory features in the general population can be estimated and this remains unknown

The mechanism of production of nonejection clicks and murmurs of mild mitral regurgitation

Review

The problem of nonejection systolic clicks and associated mitral systolic murmurs Emphasis on the billowing mitral leaflet syndrome

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Nonejection systolic clicks and the commonly associated apical systolic murmurs have aroused considerable interest since the possibility of an intracardiac origin was revived in 1961 by Reid[1] and confirmed[2,3] shortly thereafter In addition to numerous papers[4-6] relating to aspects of cases in which these auscultatory features have been detected, several large series or reviews have been published[27-30] In this review factors which have been well demonstrated and are now generally accepted are discussed in less detail than are unsolved problems and those observations which have been variously interpreted

Extracardiac clicks

Clicking sounds, often multiple and with no constant relationship to the cardiac cycle so that they occur during systole or diastole, have long been recognized as features of mediastinal emphysema[37] or pneumothorax[38] Such clicks are of very high frequency and have a superficial crackling quality The accompanying signs of the mediastinal emphysema or pneumothorax should be readily apparent and those high pitched sounds are unlikely to be confused with the intracardiac clicks which serve the basis of this review In 1913 Gallavardin[31] observed pleuropericardial adhesions at necropsy in three patients who had had mid late systolic clicks and he ascribed the clicks to these His observations formed the basis of the belief held for many years that mid late systolic clicks were innocent or had an extracardiac origin[40,41] Although Gallavardin had detected no evidence of intracardiac pathology in his patients it seems likely that a mild abnormality of the mitral valve mechanism could have been overlooked

Nonejection systolic clicks

Whereas intracardiac nonejection systolic clicks nearly always arise at the mitral valve mechanism, a tricuspid valve origin has been implied[49] in some instances Nonejection clicks occurring early in systole, have also been recorded in association with congenital aneurysms of the membranous ventricular septum[50] and with aneurysms of the left ventricle[44,51,52]

Nomenclature Nonejection clicks usually occur in the latter half of systole and have therefore often been termed mid or mid late systolic clicks When we realized that the clicks could move to early systole or occur only in early systole we regarded these terms as unsuitable Because 'ejection' systolic click is the accepted terminology for the high pitched sounds which arise at or above the aortic and pulmonary valves respectively, we introduced[3] the term 'nonejection' and it would seem to us that this remains the most suitable descriptive term for all systolic clicks which are not 'ejection' Other terms have significant disadvantages Systolic gallop[41,43,44] is unsuitable since the cadence is seldom that of a 'gallop 'Mitral click[36] would be inaccurate if the click does not arise at the mitral valve Similarly, "chordal snap'[1] would be incorrect if the click has a leaflet[3] rather than a chordal origin Leatham introduced the term post ejection[54,55] which is hardly suitable since the timing of nonejection clicks may be similar to that of ejection clicks[3,23,28,33,35]

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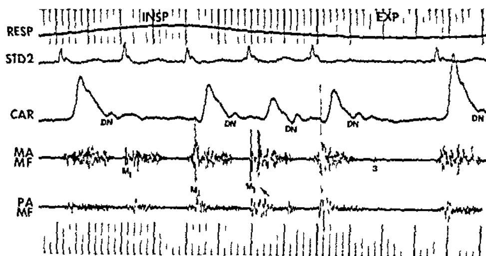


Fig 1 Phonocardiogram recorded during respiration of a 64 year old man with ruptured chordae tendineae to the posterior leaflet The crescendo-decrescendo systolic murmur of pure severe mitral regurgitation is shown The mitral component (M) of the first heart sound varies in intensity After one short diastole a second major left sided component (arrowed) of the first sound is recorded which is caused we believe by asynchronous maximal tension on the two mitral leaflets and their chordae at that time (see text) *CAR* = indirect carotid pulse tracing *DN* = dicrotic notch *MA* = mitral area *PA* = pulmonary area *MF* = medium frequency *3* = third heart sound. Time lines = 0 04 sec

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Underlying etiology In an analysis of 220 patients who presented with the auscultatory features of a late systolic murmur a nonejection click or both [28] a number of conditions were thought to be responsible for the pathology of the mitral valve mechanism (Fig 2) Most of these etiologic factors have been mentioned or confirmed in other reports [18 3 23 26 6 72] Conditions which are not represented in Fig 2 but which may result in these auscultatory features arising at the mitral valve include congestive cardiomyopathy [3] subvalvar left ventricular aneurysm [7] myocarditis [75] and atrial myxoma[27 3] (Fig 3)

Prevalence Contrary to a previously expressed opinion from this laboratory [7] we now realize that nonejection clicks and to a less extent late systolic murmurs are common findings in routine cardiologic practice We have learned as have others [3 35 36 53] that when these auscultatory features are specifically sought an ever increasing number of subjects are found to have them Subsequent to our reported 220 patients [2 43] we have encountered more than 200 patients in this Clinic the majority of whom were referred because of symptoms or for the elucidation of auscultatory signs or abnormal electrocardiogram (ECG) These numbers do not provide data from which the prevalence of the auscultatory features in the general population can be estimated and this remains unknown

The mechanism of production of nonejection clicks and murmurs of mild mitral regurgitation

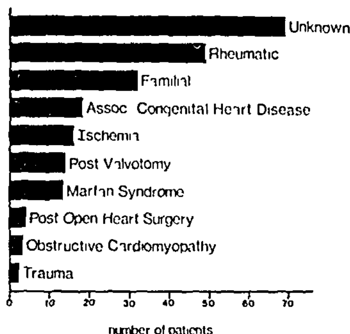


Fig 2 Probable etiology of the mitral valve pathology and associated factors in 220 patients with a *late systolic murmur* nonejection click or both Two sisters with *secundum atrial* septal defects are included only in the familial group

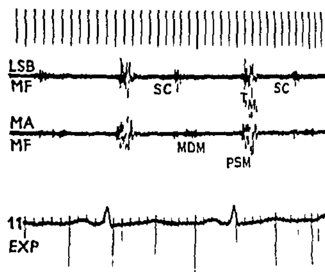


Fig 3 Phonocardiogram recorded in held expiration (*EXP*) of a man with a left atrial myxoma shows a soft nonejection click (*SC*) in mid late systole Reversed splitting of the major components of the first sound is caused by marked delay (Q M interval = 0 13 sec) of the left sided (M_1) component. A presystolic murmur (*PSM*) and short mid diastolic murmur (*MDM*) are present The click disappeared after removal of the tumor *LSB* = left sternal border T_1 = tricuspid component of first heart sound

In 1960 Leatham[76] stated that the murmur which is confined to late systole is likely to be entirely innocent for this curious timing does not fit our present knowledge of hemodynamics However, if the duration and configuration of a mitral regurgitant murmur depended only on the systolic pressure difference between left ventricle and left atrium, it would always be crescendo decrescendo with maximal accentuation near mid systole when left ventricular pressure is at its peak and the pressure difference between the two chambers potentially greatest The systolic murmur is, in fact, crescendo decrescendo in pure severe mitral regurgitation as is seen with ruptured chordae tendineae[77,78] It seems to us that the configuration of all other systolic murmurs of mitral regurgitation must depend on functional anatomic factors which affect the time of maximal regurgitation[1,28,81] Late systolic regurgitation has been confirmed cineangiocardiographically in patients with a late systolic murmur[8] and the murmur invariably increases in intensity after phenylephrine injection[2,3] A murmur confined to early systole is also not uncommonly associated with a nonejection click[36] but confirmation that this early systolic murmur does indeed denote mitral regurgitation has not always been entirely convincing either by left ventricular cineangiography[7] or in our experience by the use of phenylephrine However, we have been impressed by the observation that murmurs which are early systolic in the supine position may become late on standing and that several patients with an early systolic murmur when first seen have a murmur confined to late systole at some subsequent examinations

Like murmurs arising at other sites in the heart mitral systolic murmurs may develop a musical intonation The musical vibrations may occur throughout systole or be confined to early or late systole[3,61] They usually vary markedly in intensity and are often loudest during inspiration[3] The mitral origin of these 'honks' or 'whoops'[11,35,61,82] has been confirmed by both intracardiac phonocardiography[3,10,11] and left ventriculography[11,61,82] Some patients become disturbed when they hear their own loud musical murmurs but these 'whoops' seldom have an ominous significance and we have not observed them either to precede valve rupture or to develop more commonly during or after infective endocarditis

The mitral valve mechanism is complex and the papillary muscles chordae tendineae, annulus and leaflets as well as the size of the left ventricular cavity, are all important in maintaining competence of the valve[81,83,85] throughout or during part of systole In 1969 *Reid*[84] argued that late systolic regurgitation *could* be explained by hemodynamic rather than *anatomic*

factors However, if pressure and flow phenomena alone were responsible for confining the murmur of mild mitral regurgitation to late systole then where functional anatomic factors are not relevant as in small ring leaks of prosthetic valves or mildly leaking aortic homograft and xenograft valves in the mitral position such mitral regurgitation should also produce a late systolic murmur To our knowledge a late systolic murmur has not been reported under these circumstances nor has one been observed by us The alteration of a late systolic murmur to one which is pansystolic with a premature ventricular beat confirms the complex functional anatomy of the mitral valve

Criley and associates were the first to report from their cineangiocardiographic studies that a billowing posterior mitral leaflet reached the peak of its prolapse at the time of the nonejection systolic click We have thought [3] that the click results from elongated and functionally unequal chordae being put on stretch at the time of such maximal prolapse This postulate is compatible with the recording in some instances of an incisura on the apex cardiogram [30, 6, 87, 8] which is synchronous with the click The incisura reflects the tugging of chordae on papillary muscles at the time of peak prolapse of the mitral leaflets which is as will be discussed later our explanation for the so called systolic contraction ring [6, 8] of the left ventricle seen on cineangiocardiography A carotid pulse wave retraction [63] may also be recorded and coincides with the click The falling pressure in the carotid artery would rise immediately after maximal prolapse of the mitral leaflets because left ventricular ejection should then increase We favor that early nonejection clicks well exemplified by those occurring after mitral commissurotomy[3] [8] in relatively rigid valves with some shortened chordae result from the functionally unequal chordae being put on stretch earlier in systole Furthermore the earlier movement of mid late nonejection clicks when left ventricular end diastolic volume is decreased[1] by amyl nitrite inhalation the straining phase of the Valsalva maneuver or the adoption of the standing position has been noted to coincide with an earlier[6] and greater[9] prolapse of the posterior mitral leaflet None of these observations negates the postulate of Dock[33] that a nonejection click arises in the leaflets themselves at the time of maximal prolapse The fact that we have observed nonejection clicks after the insertion of artificial chordae[3] also does not disprove Dock s postulate

The earlier movement of both nonejection clicks and late systolic murmurs with any hemodynamic alteration which causes a decrease in left ventricular diastolic volume[3, 2] has also been observed by others [6, 9, 0, 32, 62, 6, 87] Left ventricular systolic pressure changes do not have a constant effect on nonejection clicks but alter the intensity of a late systolic murmur [28] Where left ventricular pressure is increased without significantly changing left ventricular end diastolic volume such as after the administration of phenylephrine [93] the murmur becomes louder but remains in late systole The systolic murmur becomes softer as well as earlier immediately after amyl nitrite inhalation or during the straining phase of the Valsalva maneuver because both left ventricular volume and pressure decrease However when left ventricular end diastolic volume is decreased by standing a maneuver in which left ventricular pressure is more or less maintained and myocardial contraction more forceful due to catecholamine secretion [9] the systolic murmur becomes earlier and is usually louder longer and sometimes pansystolic The systolic murmur also becomes earlier louder and longer with the inotropic effect produced by anxiety [8] or drugs such as dopamine[31] and isoproterenol.[2] Perhaps of more clinical importance than the alteration in the timing or intensity of these auscultatory features with vasoactive maneuvers is the fact that nonejection systolic clicks and also late systolic murmurs may be audible only after a postural change [3, 38, 5] Repeated auscultation in the supine left lateral standing and squatting positions may be necessary before the presence of a nonejection click or a late systolic murmur can be excluded

The billowing mitral leaflet syndrome—a specific entity

It is now readily apparent that there is a specific syndrome which consists essentially of an abnormality of the mitral valve in that the leaflets or part thereof primarily the posterior one are voluminous An attempt should be made to identify this specific syndrome and to differentiate it from other pathologic processes involving the mitral valve mechanism which may have

similar auscultatory and other *manifestations*. The syndrome may be suspected or *detected* by one or more of the following principal features: a nonejection click or clicks with or without a murmur of mild *mitral regurgitation* which is *most typically late systolic* but may be confined *to early systole, abnormal T wave* patterns on the ECG, *arrhythmias or* conduction defects, and intermittent chest pain, commonly fleeting and *atypical for angina pectoris*. Palpitations and anxiety are other common symptoms. The syndrome is more prevalent in females[11, 33] and a familial occurrence will often be detected when sought.

Nomenclature. In 1962 Humphries and McKusick[98] although favoring a pericardial origin detected the association of the ECG and the auscultatory features and referred to a "characteristic electrocardiographic auscultation syndrome." Subsequent to the recognition[3, 7, 8] of the *mitral valve* abnormality in this specific syndrome, as well as the familial factor in some instances, various descriptive terms have been applied. These include the "billowing posterior mitral leaflet syndrome,"[17, 2, 11] "systolic click-late systolic murmur syndrome,"[3, 82, 97] "mitral valve prolapse-click syndrome,"[35] "prolapsed mitral leaflet syndrome,"[21] "Reid Barlow"[11] and "Barlow's"[11] syndrome. For the purpose of this review we shall refer to it as "the billowing mitral leaflet syndrome" (BMLS).

Identification of the BMLS. Although numerous underlying etiologic factors affecting the mitral valve mechanism may result in a nonejection click and a mitral regurgitant murmur, whether early, late, or pansystolic, a careful history and physical examination will often make the underlying etiologic factor readily apparent. There is seldom difficulty, for example, in the recognition of the Marfan syndrome, established rheumatic valvular disease, hypertrophic obstructive cardiomyopathy, congestive cardiomyopathy, or a postvalvotomy click. However it may be difficult, and sometimes impossible, to differentiate the BMLS from the "floppy valve syndrome," mild rheumatic mitral valvular disease, or occlusive coronary artery disease. It is relevant to comment on this problem before proceeding further with the discussion on the BMLS.

The floppy valve and Marfan syndromes. In 1961, Bowers[99] described an abnormal ECG pattern associated with a mitral valve deformity in the Marfan syndrome. Segal and associates[45] reported mitral regurgitation in a 16 year old girl with the Marfan syndrome and a late systolic murmur, who had had an abnormal ECG 5 years previously. It is now recognized that so called "myxomatous degeneration" of the mitral valve is common in patients with the Marfan syndrome[8] and that the extent to which the leaflets are involved may vary considerably.[36] Some patients have only an isolated nonejection click or multiple clicks, some have mild mitral regurgitation as shown by a late systolic murmur, whereas others have severe regurgitation with voluminous prolapsing leaflets and elongated or ruptured chordae tendineae. Progression of mitral regurgitation in patients with the Marfan syndrome is not always rapid.[36] Aortic incompetence and medionecrosis of the aorta may be present.[36, 100]

In 1965, Read and associates[101] reported myxomatous degeneration of the mitral or aortic valves in patients without obvious features of the Marfan syndrome and they introduced the term "floppy valve syndrome." Patients with that syndrome generally present at a younger age with significant mitral regurgitation which may be associated with aortic, pulmonary, or organic tricuspid regurgitation. It must be emphasized, however, that it would be impossible to differentiate an early case of the floppy valve syndrome which may have only a late systolic murmur or nonejection click from the BMLS.

Rheumatic mitral valve disease. Although it has been disputed,[6, 8, 31] there is little doubt that the rheumatic process affecting the mitral valve mechanism can result in a nonejection click or a late systolic murmur.[11, 3, 35, 6, 12] It is known[103] that the pansystolic murmur of mitral regurgitation caused by active rheumatic carditis may disappear when the carditis has subsided. Under such circumstances pansystolic murmurs may become confined to late systole[31, 36] before disappearing. Kalbian[102] and Cobbs[36] have challenged the classic teaching that mitral regurgitation which occurs with active rheumatic carditis, and which later disappears, is caused by the inflammatory process involving the leaflets, and Kalbian[102] has postulated that temporary papillary muscle dysfunction, due to rheumatic coronary arteritis, would explain this phenomenon. However the mitral annulus is frequently very dilated in children with severe rheumatic

mitral regurgitation[1,3 ... 105] and it seems probable that such annular dilatation is the end result of involvement by the rheumatic process which we have found sometimes spares or only mildly affects the leaflets themselves Earlier in the course of this pathologic process or where the active rheumatic carditis is mild it is possible that the physiologic decrease in size of the annulus during ventricular systole is partly or entirely lost and that this feature could well be reversible Thus annular dysfunction may play an important role in transient or partly reversible rheumatic mitral regurgitation

We frequently have difficulty in assessing whether an isolated non ejection click or a late systolic murmur is on a rheumatic basis or due to the BMLS When siblings or other relatives have similar auscultatory features this usually favors the BMLS However both the BMLS and rheumatic heart disease have occurred in the same family[3] While Cobbs[35] accepts that a late systolic murmur is a not uncommon manifestation of rheumatic mitral valve involvement he considers that an accompanying nonejection click is rare Excluding the postcommissurotomy nonejection clicks we [33] and others [2 ... 82] have certainly encountered nonejection clicks and late systolic murmurs associated with established rheumatic mitral valve disease

We have not observed an abnormal ECG such as is seen in the BMLS in patients with a nonejection click or late systolic murmur in whom the underlying etiology was definitely rheumatic The reason for this is difficult to comprehend especially if the recent echocardiographic evidence of mitral valve prolapse in rheumatic cases [6] is correct

Rheumatic heart disease remains prevalent among all sections of the population of South Africa particularly the urban Black and Indian In a recent survey from this Unit [7] of 12 050 Black schoolchildren the over all prevalence of rheumatic heart disease was 6 9 per 1 000 Double this number of children however had a late systolic murmur nonejection click or both and these were the commonest abnormal auscultatory findings in that survey We suspect thay many of these children have early rheumatic mitral disease rather than the BMLS

Occlusive coronary artery disease The concept of papillary muscle dysfunction due to occlusive coronary artery disease was introduced by Phillips and associates[1,8] and has subsequently received wide acceptance[14 23 30 10 113] They had appreciated that the systolic murmur of papillary muscle dysfunction was often not pansystolic although they later[8] were reluctant as were Jeresaty[35] and Cobbs[34] to accept that a nonejection click can result from occlusive coronary artery disease It is understandable and acceptable to us however that papillary muscle dysfunction from occlusive coronary artery disease could cause functional lengthening of chordae tendineae thus abnormal billowing of one or other mitral leaflet and result in a nonejection click Taylor and co workers[11] have shown in dogs that selective papillary muscle injury produced by ethanol injection results in a greater degree of movement of the mitral leaflets in the areas subtended by the inactivated papillary muscles with a tendency to bulge back into the left atrium during ventricular systole In 1968 we reported[78] nonejection clicks and late systolic murmurs due to ischemic heart disease This has since been confirmed by other investigators [2 30 32 109 ... 0 112 113] and we now favor that these auscultatory features are common in occlusive coronary artery disease We believe that papillary muscle dysfunction may progressively affect mitral valve anatomy and function If part of a leaflet billows because of inadequate papillary muscle contraction there is then abnormal tension on that as well as the other papillary muscle and hence superimposed secondary papillary muscle damage This in turn could result in further leaflet prolapse

Features of the billowing mitral leaflet syndrome

Prevalence At the present time the prevalence of the BMLS is unknown Rizzon and co workers auscultated 1 009 female students and detected the auscultatory features in 0 33 per cent We[1,7] found them in 1 4 per cent of Black schoolchildren but emphasize that rheumatic heart disease is prevalent in that population group An assessment of prevalence in different ethnic groups would require surveys in which the investigators must be experienced in the detection of soft and intermittent nonejection clicks and non pansystolic mitral murmurs

Like any other cardiac unit we are frequently referred patients with clinically normal hearts for the elucidation of abnormal ECG s arrhyth

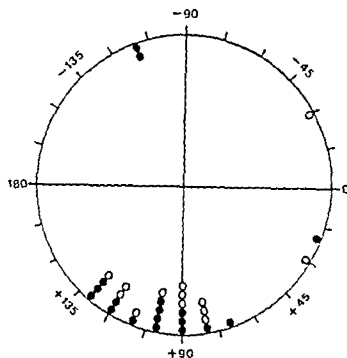


Fig 4 Mean frontal plane QRS axis of 31 patients with a secundum atrial septal defect and associated BMLS The closed circles represent patients mentioned in earlier publications Five patients with an indeterminate axis are not represented

mias or symptoms such as palpitations syncope and chest pain We find as do others an ever increasing incidence of a nonejection click in such instances

Familial occurrence Since the observation[1] a decade ago of an hereditary factor in the BMLS the familial occurrence has been well established

We have not examined the relatives of the majority of our patients and an accurate estimate of the familial occurrence cannot be made In 85 of our patients involving 26 families, an hereditary factor is present and an autosomal dominant mode of inheritance is apparent No chromosome abnormalities were detected in a family investigated by Stannard and Rigo but to our knowledge extensive chromosomal studies have not been undertaken in the BMLS

Association with congenital heart disease particularly secundum atrial septal defect Although an association between nonejection clicks or late systolic murmurs with congenital heart disease was observed shortly after the mitral origin of these auscultatory features was appreciated it is now apparent that the association with secundum atrial septal defect is common We have encountered 36 patients with secundum atrial septal defect who have one or both of these auscultatory features

We have not found any specific features on their ECG's which differentiate them from those of other patients with secundum atrial septal defect Abnormal T waves in the inferior leads similar to those found in the BMLS were present in six of the last 17 patients whose ECG s we analyzed This pattern was sometimes present before a systolic click was heard and others have detected mitral leaflet prolapse by cineangiocardiography in cases of atrial septal defect in which auscultatory features of the BMLS were reputedly absent The relevance of these T wave changes as an index of the presence of the BMLS could probably be assessed only after mitral leaflet billowing has been sought by echocardiography or left ventriculography in a large number of patients with an atrial septal defect There are other causes of mitral regurgitation in association with secundum atrial septal defect, such as rheumatic heart disease and congenital cleft leaflets but it seems to us that in most cases the mitral regurgitation is due to the BMLS that the degree of regurgitation remains mild and that surgery to the mitral valve is seldom necessary We have not encountered (Fig 4) left axis deviation of −60 degrees as reported by Victorica and associates which would be highly compatible with an ostium primum defect

Cineangiocardiography Left ventricular cineangiocardiography confirmed that late systolic murmurs denote mitral regurgitation[2] and showed that there is associated billowing of the posterior leaflet of the mitral valve Criley and associates demonstrated billowing of the posterior leaflet in patients with an isolated nonejection click and stated that the click occurred at the time of maximal billow However Cobbs has seldom seen abnormal billowing in patients with an isolated nonejection click Morphologic and angiographic studies by Wigle and co workers have shown that the posterior mitral leaflet is divided into a large middle scallop and smaller anterolateral and posteromedial commissural scallops an observation confirmed by Jeresaty Prolapse of the anterior leaflet can also be detected on cineangiocardiography and this is best demonstrated in the left anterior oblique projection Associated prolapse of tricuspid valve leaflets has been reported

Based on cineangiocardiographic appearances of left ventricular configuration some authors favor that segmental left ventricular asyner

gy[4 116 1] or so called systolic constriction[1] or "contraction ring[5 90] or a cardiomyopathy"[127] is the primary abnormality in the BMLS However increased traction from billowing leaflets on the papillary muscles could explain these appearances The different types of left ventricular systolic contraction patterns[26] such as ballerina foot hourglass or cavity obliteration would then depend on which papillary muscles were chiefly involved Myocardial function studies have usually been normal or near normal[1] The recent report[1] of the prompt return almost to normal of the left ventriculogram after excision of a prolapsing mitral valve confirms this explanation and we agree with Cobbs[6] that implication of the myocardium as the primary factor in the BMLS is implausible

Echocardiography We have little experience of this important noninvasive technique which is clearly contributory in the investigation of the BMLS Prolapses of either the anterior or posterior leaflet or of both have been identified[4-31] Popp and co workers[3] describe two echocardiographic patterns which correlated with anatomic or angiographic evidence of redundancy *of the mitral valve In both there was a posterior* systolic movement of the valve comprising a smooth U shaped wave starting in early systole in *one and in the other* an abrupt posterior motion starting in mid systole (mid systolic notch) resembling a question mark turned approximately 90 degrees clockwise Apparent separation of the anterior and posterior leaflets which has been thought to indicate mitral regurgitation did not correlate with angiocardiographic evidence of this *While false* negatives may occur echocardiograms are a reliable indication of mitral valve prolapse and according to Popp and *associates*[3] this can be detected in some patients who present with arrhythmia or chest pain and in whom auscultation and coronary arteriography are normal

Apex cardiography An abnormal systolic retraction of the apical impulse occurring synchronously with a nonejection click may be recorded[5 7 3] Spencer and associates did not observe a consistent relation between the severity of mitral regurgitation and the presence or absence of *systolic retraction* whereas there was one between the severity of leaflet prolapse and the systolic retraction Their observations are in accord with the hypothesis that the systolic retraction results from tugging of chordae on papillary muscles at the time of peak prolapse of the leaflets To our knowledge systolic retraction has not been recorded without an audible nonejection click and Spencer and co workers[5] did not find a correlation between the loudness of the click and the presence or absence of systolic retraction

Infective endocarditis Infective endocarditis can certainly supervene in the BMLS[17 15 2 55 5 3 137] and may result in the development of severe mitral regurgitation[15 55 9] A late systolic murmur had been present in most reported cases but infective endocarditis has also occurred with an isolated nonejection click[1 131 38] Such clicks may be soft and intermittent so that the diagnosis of infective endocarditis may be delayed[5] unless this auscultatory sign is carefully sought

Allen and associates followed 62 patients with a late systolic murmur 33 of whom had a nonejection click for 9 to 22 years Five developed infective endocarditis one of whom died and in another the mitral regurgitation became severe They emphasized the risk of bacterial endocarditis in patients with an isolated late systolic murmur Hayward[17] recently stated that the value of antibiotic prophylaxis against infective endocarditis has yet to be confirmed *but* commented that "in our present state of knowledge it seems obligatory to use prophylactic antibiotics for those at risk Our current policy is to advise prophylaxis against infective endocarditis in all patients with a nonejection click or late systolic murmur but this approach may be modified[95] in the future

Atypical chest pain Chest pain is common in the BMLS[4 1 3 5 7 2 23 3 35 36 6 8 8 8 9] The pain is sharp precordial without a constant relationship to effort or emotion and is usually of short duration However it may sometimes resemble ischemic pain Chest pain is commonly the presenting symptom and many patients are admitted to hospital with suspected occlusive coronary artery disease Both Cobbs[31 34] and Jeresaty[5 9] *have postulated* that it is due to abnormal tension on papillary muscles Compatible with their postulate is the finding of Le Winter and *associates*[40] *that* pain was induced in eight of nine patients by the injection of phenylephrine The transitory nature occurrence at rest and the fact that it may disappear for months without treatment are difficult to

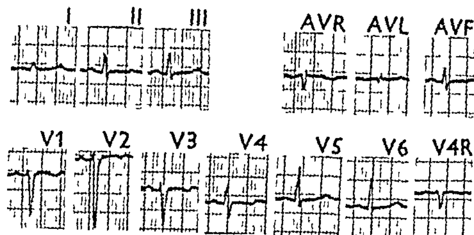


Fig 5 ECG of a 29 year old woman with an intermittent soft nonejection click. There is inversion of the initial part of the T wave in Leads V_4. The T waves are flattened in Leads II and aV_F

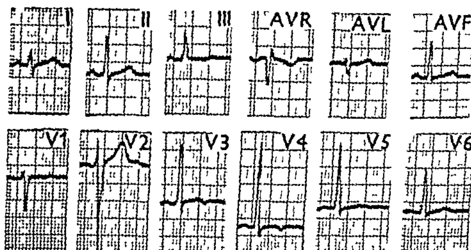


Fig 6 ECG of a 28 year old man with a soft nonejection click and early nonpansystolic murmur The T waves in Leads V_4 and V are terminally inverted

explain We agree with Jeresaty[35] that this syndrome is probably a more common cause of chest pain than other etiologies which are invoked to explain pain in the absence of coronary artery disease ' The BMLS is nevertheless frequently missed by many physicians including cardiologists who remain unaware of its features and inexpert in detecting the auscultatory signs

Psycho neurotic manifestations We are impressed with the number of patients who appear extremely anxious, some of whom fulfil the criteria of Da Costa's syndrome[141] or neurocirculatory asthenia[142, 143] Hancock and Cohn[9] described symptoms of seemingly neuropsychiatric origin' and Cobbs[36] has encountered narcotic addiction in several patients in whom occlusive coronary artery disease had been diagnosed because of abnormal ECG tracings Jeresaty[35] also commented on the frequency of mental disturbances In our experience, many patients had sought medical advice because of severe chest pain They were at first reassured that their hearts were normal but when the pain did not subside they were told that they were ' neurotic It seems to us that this is not "reassuring to those who are suffering the pain, which is frequently associated with disturbing palpitations, and that anxiety may then supervene

Electrocardiographic features The prevalence of ECG abnormalities in the BMLS varies in different series[9, 28, 30, 32, 33, 35, 62, 1 6] depending on the selection of cases, and the exact prevalence is unknown Fifty three (37 per cent) of our last 144 patients with the BMLS had an abnormal ECG 32 of whom had the most widely recognized pattern[3, 6, 7, 9, 13, 15, 16, 7, 28, 30, 3, 33, 35, 61, 64, 66, 69, 8, 90, 116, 139, 144] of an inverted or partially inverted T wave in Leads II III, and aV_F with resultant abnormally wide mean frontal plane QRS T

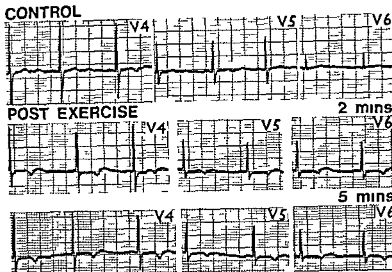


Fig 7A Terminal notching of the T wave in a 14 year old girl with a late systolic murmur and a click After effort there is slight T wave inversion the nadir of which is at the same point on the T wave as the notch in the control tracing

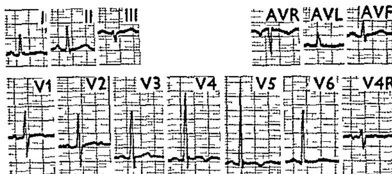


Fig 7B ECG of a 30 year old top class rugby football player shows terminal notching of the T waves in Leads V Deepening of the notch in Leads V and V results in T wave inversion The QRS voltages in the precordial leads are compatible with biventricular hypertrophy—a recognized feature of the athlete s heart

angle The ST segment is usually normal slightly elevated or only mildly depressed with an upward convexity With increased experience of the BMLS we have encountered similar T wave abnormalities in the anterior leads In six of our 144 patients these were confined to the right mid or mid and left precordial leads whereas anterior T wave changes were associated with the typical pattern in the inferior leads in 14

Diffuse T wave inversion has been observed by Shell and associates and ourselves[33] but is uncommon T wave inversion may be complete or partial involving either the initial (Fig 5) or terminal (Fig 6) portion Prominent upright U waves are quite common [4 8] especially in the right precordial leads In some instances we have noted a distinctive notching of either the upstroke or the terminal part (Fig 7A and B) of the T wave in the precordial leads Deepening of the notch until the T wave is completely inverted may develop in the absence of obvious cause or after effort (Fig 7A) The ECG may alter spontaneously [3 6 3] (Fig 8) and an appearance of inferior or anterior ischemia may be replaced by a normal pattern within a period of 30 minutes Jeresaty has demonstrated the development or worsening of inverted T waves after amyl nitrite inhalation and others[3] have made similar observations after the adoption of the erect position However similar T wave changes have been recorded after amyl nitrite in young pilots with no abnormal cardiac signs [1 5] In one of

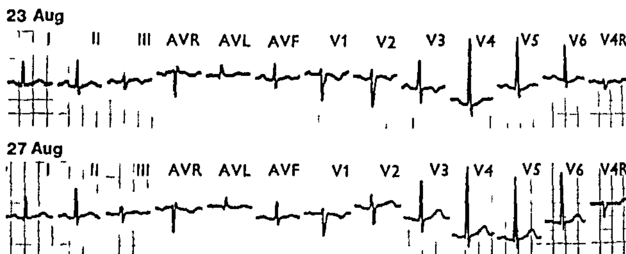


Fig 8 Spontaneous alteration of the ECG of a 13 year old girl with the BMLS on a familial basis In the second tracing (Aug 27) the T waves are upright in Leads V and V, and are no longer flattened in the left precordial leads

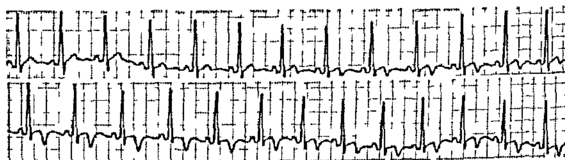


Fig 9 Continuous Holter recording of the 28 year old man whose ECG is shown in Fig 6 Progressive T wave inversion and return to normality within 2 minutes occurred several times during the period of monitoring apparently unrelated to emotion exercise or change in heart rate

our patients Holter monitoring showed several episodes of progressive T wave inversion with return to normality, unrelated to any specific activity or to emotion (Fig 9)

The T waves usually normalize immediately after strenuous effort In the 2 and 5 minute postexercise tracings they often revert to the control pattern but the T wave inversion may deepen In some instances where the resting ECG is normal the abnormal T wave pattern is produced by exercise In others the T wave inversion present in some leads at rest becomes more widespread after effort We encountered flat ST segment depression with a sharp ST/T wave angle, worsening after effort, resembling that described in women with angina pectoris and normal coronary arteriograms[146, 147] in one woman, aged 40 years, and have no means of differentiating this pattern from that of ischemic heart disease

Unlike others[9, 117, 124] we have seldom observed prolongation of the Q T interval in the BMLS In our recent analysis of 144 new patients only one, a 38 year old woman, had a slightly prolonged Q T (0 47 sec)

Many patients with abnormal ECG s complain of fleeting sharp left sided chest pain, but occasionally the pain resembles angina in its character site, and relationship to effort or emotion It is noteworthy, however, that identical ECG patterns have been seen in *asymptomatic* subjects and that others with normal ECG s both at rest and after effort, complain of pain Jeresaty[35] reported abnormal T waves in at least eight patients who had prolapsed leaflets on cineangiocardiography and in whom the auscultatory findings and selective coronary arteriograms were normal In symptomatic or asymptomatic patients without abnormal auscultatory signs, we have suspected the BMLS on the basis of an abnormal ECG, and at a later examination such patients have frequently had a click or a late systolic murmur A few possibly have 'silent prolapse'[15, 36] but in our opinion the auscultatory features will sooner or later be detected by careful and repeated auscultation

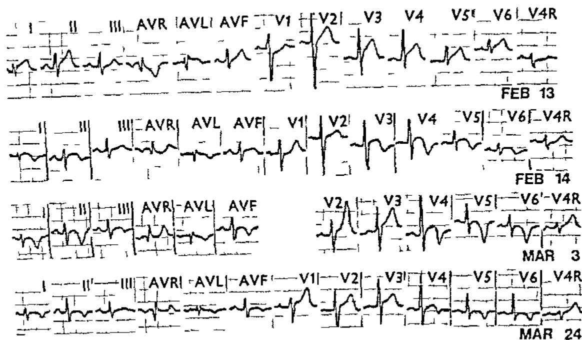


Fig 10 Serial tracings of the 21 year old man with the BMLS on a familial basis show the evolution of an anterolateral myocardial infarction One year later the ECG had reverted to normal.

The cause of the ECG changes remains ill understood We have already mentioned that some investigators favor primary myocardial dysfunction " Although we agree that this is relevant in occlusive coronary artery disease with papillary muscle dysfunction primary valvular pathology is far more probable in the BMLS Selective coronary arteriograms have almost invariably been normal and thus our earlier hypothesis that the circumflex branch of the left coronary artery may become occluded as a result of distortion seems to have been disproved A recent postulate by Gentzler and associates based on a selective coronary arteriographic study of congenital absence of this artery has not been confirmed Corkscrew coronary arteries have been observed but their significance if any is uncertain In 1970 we suggested[7] that increased traction from chordae attached to a billowing leaflet might interfere with the rather tenuous vascular supply of the papillary muscle which in turn could cause ischemia or infarction of that papillary muscle and adjacent myocardium This suggestion of abnormal tension damaging a papillary muscle has independently been made by Cobbs [34] and Jeresaty[5] Increased tension on papillary muscles would be compatible with the observation that T wave inversion develops or becomes more marked with standing or amyl nitrite inhalation both of which result in increased prolapse of the leaflets[33] Two of the eight patients in whom chest pain was produced by phenylephrine had nonspecific ST segment and T wave changes but it was not made clear whether these were induced by the phenylephrine It is now well documented[1] [5] that myocardial infarction may occur in the absence of demonstrable arteriographic abnormality of the coronary vessels and we wonder if the myocardial infarction could ever be a direct complication of the BMLS Could increased tension on papillary muscles cause coronary artery spasm the role of which in acute myocardial infarction has yet to be elucidated? Alternatively retrograde propagation of thrombus from an occluded vessel in the papillary muscle might infarct the adjacent myocardium[33] We have encountered two young men aged 21 and 24 years respectively with nonejection clicks a classical history of acute myocardial ischemia and both ECG (Fig 10) and enzyme confirmation of infarction Selective coronary arteriography is normal in one and in the other (aortogram only) the anterior descending branch of the left coronary artery has a corkscrew appearance Neither man has any of

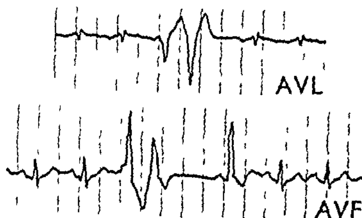


Fig 11 Multifocal ventricular ectopic beats which occurred immediately after strenuous exercise in the young woman whose ECG is shown in Fig 5

the accepted risk factors which predispose to ischemic heart disease A nonejection click is present in a sibling of each, and the 46 year old mother of one has an early nonpansystolic murmur of mitral regurgitation

We think it probable that the BMLS accounts for a number of examples of so called 'nonspecific ST and T wave changes[134] including those which have been attributed to the syndrome of the suspended heart[155, 156] anxiety,[157] and neuro circulatory asthenia (Da Costa s syndrome)[141, 143] Nonspecific T wave changes resembling those of the BMLS have also been reported[11, 159] in highly trained athletes These T wave abnormalities often, but not always, normalize transiently after exercise In one athlete the ECG became normal after he had stopped training[15] The ECG features of the athlete's heart are unexplained but effects of increased vagal tone in conjunction with shifts in myocardial potassium have been suggested[158] During the last 2 years four very fit and completely asymptomatic young men and a 58 year old marathon runner were referred to us because of ECG abnormalities detected on routine examination, for either life insurance or aviation purposes All had soft intermittent nonejection clicks on careful auscultation We do not understand these observations but suggest that T wave abnormalities (Fig 7 *B*) in some athletes are related to minimal abnormal billowing of their mitral leaflets The relationship of physically fit asymptomatic young men with marked T wave abnormalities to symptomatic patients with ECG and other features of the BMLS requires elucidation

Whatever the underlying basis of the ECG in the BMLS it is difficult to account for the lack of correlation between symptoms, intensity of the auscultatory signs, extent of the ECG abnormality, and the severity of mitral valve prolapse

Arrhythmias and conduction defects A wide variety of arrhythmias have been encountered and include supraventricular tachycardia,[29, 32, 1, 6, 149] atrial fibrillation,[9, 1, 30, 31, 35, 36, 139, 149] atrial flutter,[9, 36] atrial ecotopic beats,[9, 28, 32, 61, 125, 126, 140, 149] ventricular tachycardia[9, 73, 85, 125, 1, 6] and ventricular fibrillation[117, 124] Premature ventricular contractions (Fig 11) are the most common rhythm disturbance[9, 17, 24, 30, 3, 33, 35, 64, 85, 125, 126, 139, 140, 149] and may be unifocal or multifocal and display the R on T phenomenon They are often precipitated or aggravated by emotion and exercise[11, 33, 126, 149] Ventricular ecotopic beats may occur with an otherwise normal ECG, irrespective of whether they are uni or multifocal or whether they are present at rest or only after exercise[17, 31, 126, 143] We favor that ventricular arrhythmias could be caused by abnormal tension on papillary muscles with secondary papillary muscle and adjacent myocardial ischemia but atrial arrhythmias would be difficult to explain on that basis Wit and associates[161] have demonstrated spontaneous diastolic depolarization of muscle fibers in the anterior mitral leaflet of the dog when these were stretched or exposed to catecholamines and they suggested that the mitral valve could act as a site of ectopic impulse initiation Possibly a similar mechanism in man could explain some of the atrial arrhythmias in the BMLS in which there is considerable stretching of the leaflets

Conduction disturbances have also been observed and include sinoatrial block[161, 162] present in two of our patients and left[29, 31] and right[11, 140] bundle branch block Prolongation of the P R interval has been reported[30, 31, 140] and among our last 144 patients was present in seven, aged 18 to 46 years either at rest or after effort Although 'an increased incidence of left axis deviation was encountered by Willems and associates[31] this is uncommon in our experience and only two of the 144 patients men aged 43 and 46 years had left axis deviation to −70 and −50 degrees respectively

The mechanism of these conduction disturbances also requires clarification Possibly there is interruption of the conduction system as a result of fibrosis in the myocardium as was observed at necropsy in one patient[18] Alternatively the small

coronary vessels supplying the sinus and atrioventricular nodes the His bundle or its branches may be involved by a degenerative process similar to that reported by James[63] in the Marfan syndrome Whatever the mechanism it is important to identify a conduction disturbance as the possible cause of palpitations or syncope prior to starting treatment with beta adrenergic receptor blocking agents

Treatment and prognosis Chest pain and palpitations may fluctuate in severity and we have observed spontaneous decrease or disappearance of ventricular ectopic activity Furthermore although the pattern of T wave inversion usually remains unchanged or shows spontaneous variation there is an occasional trend toward sustained improvement[7,25] This decrease in symptoms and signs of ischemia may be a reflection of muscle necrosis and fibrosis in the papillary muscle or adjacent myocardium

We have used propranolol or other beta receptor blocking agents to treat the chest pain, usually with good effect Ventricular irritability also responds well to this group of drugs although occasionally large doses (e g propranolol 1 Gm daily) are required If control is inadequate the addition of diphenylhydantoin has been contributory Our current policy is to subject all patients with the BMLS whether symptomatic or not to a strenuous effort test and if multifocal or numerous unifocal ventricular ectopic beats develop beta blocking drugs are given in increasing dosage until satisfactory control of the arrhythmia is achieved Kremkau and associates[3] reported a 32 year old woman who required mouth to mouth resuscitation for an episode in which she was unconscious and cyanosed and had a rapid irregular pulse Her multifocal ventricular premature contractions with bursts of ventricular tachycardia were extremely difficult to control and eventually required both propranolol and permanent transvenous demand ventricular pacing Cobbs and King[2] recently subjected a patient whom they had resuscitated from ventricular fibrillation to mitral valve replacement This rather drastic therapy should very seldom be necessary but would be justified as a life saving measure

Sudden death has been reported * s but is rare and there remains a paucity of well documented cases Other conditions either associated with the BMLS or themselves causing the auscultatory features may sometimes have been relevant The two patients reported by Jeresaty[35] were relatively old and associated occlusive coronary artery disease is difficult to exclude The 39 year old man[2] who died while mowing a lawn was reputed to have normal coronary arteries at a necropsy which was not attended by us Shappel and associates[117] reported the sudden death during emotion of a 27 year old woman with a late systolic murmur and nonejection click Apart from persistent prolongation of the Q T interval the ECG was normal and only one ventricular ectopic beat had been recorded despite frequent Holter monitoring and effort ECG s Her mother and maternal grandmother had died suddenly at 32 and 40 years of age respectively Although that woman definitely had the BMLS it seems possible to us that she also had the hereditary condition of prolongation of the QT interval,[84 65] inherited on the maternal side (Fig 1 p 1129)[17] whereas the BMLS which was present in her father and her siblings was benign' Hancock and Cohn reported the sudden death of a 29 year old woman who probably had the BMLS on a familial basis Her resting ECG showed widespread T wave inversion and multifocal ventricular ectopic beats Shell and associates[15] as well as ourselves[7] have encountered patients with the BMLS in whose families instances of unexplained sudden death at a young age had occurred However details of the deaths are lacking and the reported incidence of such deaths in relatives remains small. Allen and co workers[5] unfortunately excluded all patients who had an abnormal ECG from their series because, unlike many others they apparently believe that when the ECG is abnormal there is either an associated cardiomyopathy or coronary artery disease Their conclusion that there is no justification for the belief that ventricular ectopics in these patients are dangerous would therefore seem to us to be rather tenuous

We have already discussed the importance of trying to differentiate between the BMLS and the usually more severe valve pathology of the floppy valve or Marfan syndromes On the available evidence provided infective endocarditis does not supervene the mitral valvular lesion usually progresses very slowly in the BMLS In nine patients reported by Epstein and Coulshed[2] the systolic murmur had been known to be present for at least 10 years Only one of

their 38 patients progressed to severe mitral regurgitation and was thought to have ruptured chordae tendineae. Allen and associates[11] in their 9 to 22 year follow up of 62 patients found one with spontaneous chordal rupture necessitating valve replacement and only slight deterioration in eight others. It would seem to us impossible to predict in any individual case whether progression to pure severe mitral regurgitation will occur but, in the absence of infective endocarditis, it is probable that the majority of patients deteriorate only slightly or not at all over many years.

Pathology. There is a paucity of pathologic data on patients with the BMLS because of the generally good prognosis and the mild nature of the hemodynamic disturbance. A cardiac abnormality was not detected at necropsy in the 29 year old woman of Hancock and Cohn with the BMLS on a familial basis. In the 27 year old woman reported by Shappell and associates[117] there was redundancy and thickening of both anterior and posterior leaflets, most marked in the posterior one, with extensive deposition of myxomatous material within the fibroelastic collagenous matrix. The chordae were elongated and thin. The conducting system and coronary arteries were normal but mild cystic medial necrosis was seen in the aorta. A voluminous posterior leaflet was found at necropsy in both the 39 year old man reported by us and the 63 year old woman who died suddenly 2 days after cardiac catheterization described by Trent and associates.[18] Myxomatous change was detected in the mitral valve of their patient.

We have recently encountered two patients with the BMLS who died of acute leukemia. One was a 24 year old woman with three nonejection clicks in mid late systole and the other a 6 year old girl with a late systolic murmur, nonejection click, and inverted T waves in Leads II, III, and aV_F. The leaflets, particularly the posterior one, were voluminous and in the child multiple leaflet scallops were prominent. These valves have been examined by Roberts[1] and histologic sections showed an increased amount of the spongiosa component of the leaflets and that acid mucopolysaccharide material was present. Roberts and associates[96] have pointed out that in the floppy valve the spongiosa has been described as being disorganized giving rise to what has been called mucoid or myxomatous degeneration but little information regarding normal organization of the spongiosa is available for comparison. Kern and Tucker[167] have emphasized that myxomatous degeneration is a nonspecific tissue reaction to a variety of etiologic factors which include rheumatic valvulitis[167] and aging changes.[16] The pathologic and other features of our two leukemic patients with the BMLS will be considered in more detail in a further communication.

There are now many reports[41, 87, 101 ...] of surgery for pure severe mitral regurgitation in patients, generally elderly, with voluminous mitral leaflets. The chordae tendineae are usually elongated and may be thickened or attenuated. Rupture of one or more chordae is common and sometimes initiates the deterioration. The majority of reported cases did not show stigmata of the Marfan syndrome. There was frequently a history of a murmur having been detected many years previously. In a 58 year old woman operated on for severe mitral regurgitation due to ruptured chordae[87] a late systolic murmur and nonejection click had consistently been heard during the 5[?] years prior to her sudden deterioration. There was no evidence of infective endocarditis at operation and the mitral leaflets were thin and mobile but special staining of leaflet tissue did not show myxomatous or mucoid changes. One of the five patients with mucoid degeneration subjected to surgery by Davis and associates[170] had a loud late systolic murmur and a nonejection click with typical ECG changes. That patient as well as several treated surgically by McKay and Yacoub[17] had normal preoperative pulmonary wedge and pulmonary artery pressures and we fail to understand how these findings can be compatible with the cineangiocardiographic assessment that the mitral regurgitation was severe. Nevertheless, both studies do provide further evidence that a few patients with the BMLS may progress, usually after many years, to pure severe mitral regurgitation with or without rupture of chordae tendineae.

Pomerance[165] found mucoid degeneration of atrioventricular valves in 35 subjects, an incidence of one per cent of adult necropsies. Both mitral cusps were voluminous in 23 but the deformity was more marked in the posterior leaflet and in 11 subjects this leaflet only was microscopically abnormal. Similar but lesser changes were seen in the tricuspid valve in nine patients. Microscopically, the basic abnormality was apparently degeneration of the fibrosa with

replacement by a loose metachromatically staining myxomatous tissue with fibroelastic thickening of the surrounding endocardium Pomerance postulated that loss of the normally dense collagenous supporting structure would allow stretching of the cusp by normal variations in intraventricular pressures and would result in the characteristic voluminous ballooned leaflets The majority of the subjects studied by her were male and all were more than 50 years of age The clinical findings were analyzed retrospectively and there was little correlation of murmurs heard during life with the severity of the valvular deformity

Concluding remarks

Nonejection clicks and associated mitral systolic murmurs are common in routine cardiologic practice and can result from multiple etiologic factors affecting the complex mitral valve mechanism Such factors include a specific syndrome the essential feature of which is that the mitral leaflets or part thereof primarily the posterior one are voluminous The syndrome has stimulated widespread interest and study during the last decade and various descriptive terms including the billowing mitral leaflet syndrome (BMLS) have been applied to it A familial occurrence of the BMLS may be detected and symptoms include chest pain palpitations syncope and anxiety Arrhythmias conduction defects and ECG abnormalities which mimic occlusive coronary artery disease are important features which remain ill understood It is suggested that there is a possible relationship between the so called athlete s heart and the BMLS We also postulate that the entity of acute myocardial infarction without demonstrable occlusive coronary artery disease is in at least some instances a complication of the BMLS—possibly on the basis of coronary spasm

More severe mitral regurgitation infective endocarditis or rarely sudden death may supervene in the BMLS but we conclude from published data and our own experience that the prognosis is generally good

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Corrective surgery for congenital cardiovascular defects in early infancy

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Gross[1] ligated a patent ductus arteriosus in 1938 and opened the modern era of surgery for congenital heart disease The surgical attack on cyanotic lesions began six years later with the dramatic demonstration by Blalock and Taussig[2] of the salutary effect of systemic to pulmonary artery anastomosis Over the next two decades many types of palliative operations were described for a wide range of congenital lesions Palliative procedures saved the lives of thousands of children, allowing them to survive until corrective surgery was feasible

Unfortunately each palliative operation has produced its own set of complications For example systemic to pulmonary artery shunts have been associated with excessive pulmonary blood flow leading to congestive heart failure and the later development of pulmonary vascular obstructive disease[3] kinking of a pulmonary artery can result in shunt flow going to only one lung and hypoplasia of the vasculature of the other lung[4] closure of the anastomosis at the time of corrective surgery has often been associated with a high mortality rate [5] Banding of the pulmonary artery to reduce excessive pulmonary blood flow has been associated with many complications[6] severe cyanosis with polycythemia if the band is too tight continuing congestive heart failure if it is too loose obstruction of branch pulmonary artery, right ventricular obstruction hypertrophy, subvalvular aortic stenosis, erosion of the band with rupture of the pulmonary artery deformity of the pulmonary valve calcification of the pulmonary artery, and a higher operative mortality rate for ventricular septal defect (VSD) repair when a band is present than when it is not Creation of an atrial septal defect for transposition usually works well initially, but cyanosis and symptoms often return within weeks to months after palliation

For these reasons primary correction rather than palliation of congenital heart lesions has been the goal of surgeons since open heart surgery became feasible in the mid 1950 s Unfortunately, the mortality rate of babies undergoing cardiopulmonary bypass was unacceptably high Most surgeons therefore continued to do palliative rather than corrective operations in infants Parallel with the development of cardiopulmonary bypass over the past two decades however, another technique evolved which combined with cardiopulmonary bypass has recently produced a high degree of safety in corrective operations in infants deep hypothermia with circulatory arrest

Bigelow and associates[7] introduced the concept of hypothermic protection of vital organs during periods of circulatory arrest in 1950 Lewis and Tauffic[8] applied the technique clinically when they closed an atrial septal defect under direct vision during circulatory arrest with hypothermia in 1953 The method then gained more widespread clinical application and was combined with cardiopulmonary bypass in the late 1950 s Enthusiasm for hypothermic circulatory arrest however waned after the publication of a series of reports associating it with severe cerebral damage and death[9, 10]

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While the technique had fallen into disfavor in the Western world Horiuchi and co workers [1] in Japan in 1963 reported very good results for VSD closure in a group of infants undergoing surface cooling and circulatory arrest Hikasa and colleagues later reported a larger series with equally good results They made a significant modification of technique to surface cooling was added core cooling and rewarming by the use of cardiopulmonary bypass Barratt Boyes and associates reported their experience with this technique in the Western literature thus giving further impetus to the idea of corrective cardiac surgery in infancy

Conventional cardiopulmonary bypass has been used successfully in infants[4 6] the mortality rate is high however in very young infants under the age of 3 months The particular advantage of hypothermic circulatory arrest in this age group is total relaxation of the heart and the absence of intracardiac cannulas and suction devices inside the tiny cardiac chambers

The technique we now use incorporates the principle of surface cooling followed by core cooling and rewarming on cardiopulmonary bypass Cooling of the peripheral body mass is accomplished while liver and kidney are relatively warmer and are able to handle metabolic waste products during the major part of cooling Core cooling on cardiopulmonary bypass is then carried out to reduce the temperature of central organs below 20° C Initial rewarming on the pump provides early functioning of the core organs to handle the metabolic end products of the recovering body mass and minimizes acidosis At 32 to 33 C extracorporeal circulation is stopped and rewarming is completed by surface means

Clinical study

In the 2 year period between January 1973 and December 1974 we operated upon 83 infants under the age of 1 year to repair correctable congenital heart lesions All operations were performed with deep hypothermia and circulatory arrest There were 27 patients with VSD 24 with transposition of the great arteries (d TGA) 17 with tetralogy of Fallot (TOF) eight with total anomalous pulmonary venous connection (TAPVC) and seven with other lesions The over all mortality rate was 12 3 per cent

Infants under the age of 3 months pose the greatest challenge to cardiac surgery since they often have the most extreme anatomic deformities and the most severely disordered physiology furthermore they impose the technical difficulty of very small heart size The highest mortality rates for palliative operations are in this group so the potential benefits of corrective surgery are greatest We therefore confine this discussion to the 40 infants 3 months of age or younger of the total group of 83 (Table I)

Table I Infants under the age of 3 months undergoing corrective surgery

Type of lesion	*No of patients*	*Age (days)*	*Deaths*	
			No	*%*
A Correctable				
VSD	12	20 88	3	25
d TGA	7	60-90	0	0
IVS	4	60 90	0	0
VSD	3	60-89	0	0
TOF	8	12 90	1	13
TAPVC	8	1 4 85	2	25
AS	2	21 42	0	0
Total	37		6	15
B Uncorrectable				
Rhabdomyoma	1	1	1	
Truncus and A V canal	1	30	1	
VSD and primitive MV	1	65	1	
Total	3		3	100

Operative indications and methods

Our current management of infants with specific lesions is outlined in Figs 1 to 3

VSD Infants with a large VSD associated with congestive heart failure pulmonary artery pressure at or near systemic level and pulmonary blood flow more than twice systemic flow are treated with aggressive medical measures but those who cannot be discharged from the hospital undergo corrective surgery

All but one of the ventricular septa in our group of 12 infants were patched through the right atrium with retraction of tricuspid valve leaflets The exception was a septum with multiple muscular defects that were difficult to identify through the right atrium so the apex of the left ventricle was opened and two discrete defects were closed with a single patch A large

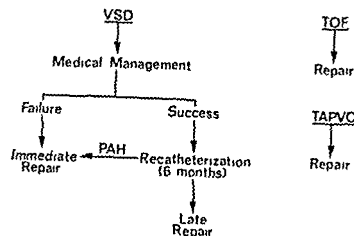


Fig 1 Surgical management of infants with VSD TOF or TAPVC

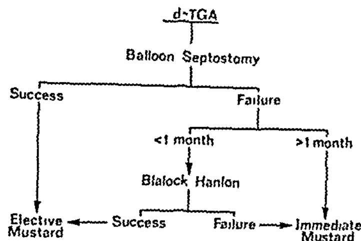


Fig 2 Surgical management of infants with d TGA

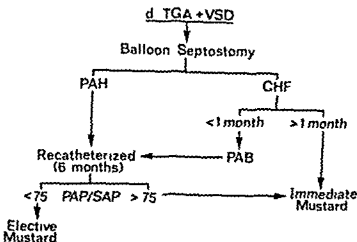


Fig 3 Surgical management of infants with d TGA plus VSD

endocardial cushion type VSD in another infant was incompletely closed deliberately to avoid heart block

d TGA Because of recent modifications in technique, our indications for choosing palliative or corrective surgery for d TGA are now in transition Our recent experiences lead us to recommend that balloon atrioseptostomy be performed routinely at catheterization of all infants with d TGA If the patient's clinical status is not improved by this procedure, or when deterioration occurs after initial improvement a Blalock Hanlon atrial septectomy should be done in patients under the age of 1 month and a Mustard operation in older infants If clinical deterioration continues after adequate septectomy a Mustard operation should be carried out at any age If palliation has been satisfactory, we recommend elective Mustard repair for most infants with d TGA at the age of 1 year because of the potential for early development of pulmonary vascular obstructive disease,[19] especially when VSD is also present

When VSD is present, balloon septostomy is routinely carried out Patients who develop congestive heart failure after the age of 1 month undergo Mustard operation, those with failure under 1 month undergo pulmonary artery banding Patients with VSD and pulmonary artery hypertension without congestive failure and those with band are recatheterized at about 6 months of age, those with pulmonary to systemic arterial pressure ratio greater than 0 75 undergo Mustard s operation with transatrial closure of VSD at that time and those with ratio under 0 75 have corrective operation at about 1 year of age

Pericardium was used for the intra atrial baffle in six patients and an elastic Dacron patch in one Two infants had obstruction of the superior vena cava at the baffle which would not be relieved by baffle enlargement Both had a side to side superior vena cava to right pulmonary artery anastomosis for caval decompression One baby s VSD was closed with a Dacron patch, the other s with interrupted sutures reinforced with Dacron pledgets

TOF Correction of TOF is carried out when the patient has documented hypoxic spells severe hypoxemia or suprasystemic right ventricular pressure The intracardiac anatomy must be unambiguous on angiography Present contraindications to corrective operation are pulmonary atresia severely hypoplastic distal pulmonary arteries, or anterior descending coronary artery arising from the right coronary artery We have not seen either severe pulmonary artery hypoplasia or anomalous anterior descending coronary artery since this study began

The VSD in each of the eight cases was closed with a Dacron patch Severe hypoplasia of the subpulmonary conus and the pulmonary annulus was present in all patients so each required the placement of a large pericardial outflow patch

TAPVC Since there is no suitable palliation for TAPVC corrective operation should be carried out when the diagnosis is made even in the first week of life Our youngest patient was 36 hours old at operation

There were eight patients in this group The two patients with connection to the coronary sinus were repaired by wide opening of the coronary sinus through its common wall with the posterior left atrium The coronary sinus orifice in the right atrium was then closed with a purse string suture and the patent foramen ovale closed thus draining the entire coronary sinus return into the left atrium and closing all inter atrial communications [7]

Four infants with supracardiac and two with infracardiac TAPVC underwent ligation of the communicating ascending or descending vein and anastomosis of the common pulmonary vein to the posterior left atrium The posterior approach with elevation of the ventricles out of the pericar dium was used in three patients the right sided approach [9, 1] was used in the other three

Miscellaneous lesions Unicommissural ste notic aortic valves in two infants were partially incised and dilated through an aortotomy

A child with VSD and congenital mitral stenosis underwent patch closure of the VSD and fenestration of obstructive interchordal primitive valve tissue

A large tumor mass produced congestive heart failure and a low output state in a 1-day old infant The tumor mass could be only partly excised at operation

Type II truncus arteriosus was found at cardiac catheterization in a severely ill neonate Because of the generally poor results of pulmonary artery banding for this condition total correction with the use of a small valve bearing aortic homograft was attempted

Results

The complications that have followed correc tive surgery are listed in Table II

VSD The patient whose endocardial cushion type VSD was closed incompletely continued to have severe congestive heart failure and 24 hours

Table II Complications after corrective surgery

Complication	No	Percent
Seizures	3	8
Arrhythmias	24	65
Wound infections	3	8
Cardiac tamponade	1	3
Retained left atrial line	1	3
Superior vena caval obstruction	2	5
Persistent atelectasis	1	3

after initial operation underwent pulmonary artery banding She has done well since this but will require a third operation One patient had a single seizure, one had transient heart block and a third had a wound infection that healed after spontaneous drainage and treatment with anti biotics A 3 month old infant had persistent ate lectasis of her right lung found to be due to bronchial stenosis The atelectasis took about 3 weeks to clear

There were no deaths in the 15 patients over 3 months of age three occurred under 3 months Two of the three deaths were probably prevent able One infant died of unrecognized cardiac tamponade and the other died of inadequately treated tachyarrhythmias that eventually led to cardiac arrest followed by a low cardiac output state for several days before death One marasmic infant died 3 days after operation having shown no improvement from the preoperative condi tion

d TGA Among the 18 patients over 3 months of age only one with intact ventricular septum and two with VSD died No patient under the age of 3 months died Follow up catheterization of one of the two babies who required cavopulmonary anastomosis showed that most of the superior vena caval (SVC) flow was under the baffle and through the mitral valve with only slight flow through the anastomosis The other child had obstruction of the SVC at the baffle but the SVC emptied poorly into the pulmonary artery The eventual fate of these anastomoses is still not known they may be functionally useful they may allow right heart recirculation from pulmo nary artery to superior vena cava or they may close spontaneously Cardiac recatheterization is planned for both infants in the future

Transient seizures occurred in one patient who

had seizures preoperatively One patient had a wound infection that healed after drainage and antibiotic treatment Despite the presence of transient arrhythmias in several patients, all had normal sinus rhythm when they were discharged from the hospital

TOF The only significant complication in this group occurred when the tip of a left atrial catheter broke off during its removal Two days after the initial surgery the catheter tip was removed from its free lying position within the left atrium under normothermic cardiopulmonary bypass, recovery was uneventful Junctional tachycardia was easily controlled with digitalis in one patient a superficial wound infection healed with local wound care in another

No deaths occurred in the nine patients over 3 months of age The one death in the group under 3 months was a 6 week old infant who developed renal failure abdominal distension and diarrhea immediately after repair He then developed low cardiac output and pneumonia and died on his fifth postoperative day The cause of death was found to be necrotizing enterocolitis which may have been related to diarrhea that appeared several hours preoperatively

TAVPC A 1 week old infant was reoperated upon on his first postoperative day for pericardial tamponade and had immediate hemodynamic improvement after drainage He then had several seizures associated with hypocalcemia that were controlled by administration of calcium and anticonvulsives

A 3 month old infant died 2 days after correction of supracardiac drainage Initially after operation, a low cardiac output state led to reoperation which disclosed no anatomic cause of the low output At postmortem examination the anastomosis was widely patent and the left heart chambers were of adequate size No cause of death was determined

A 2 week old baby with supracardiac drainage had a high left atrial pressure with low output state immediately after bypass, and died in the operating room She was found to have a small left atrium and hypoplastic left ventricle

Miscellaneous lesions Both babies with aortic stenosis recovered uneventfully

The infant with VSD and mitral stenosis had low cardiac output postoperatively despite the maintenance of high atrial pressures On the first postoperative day, excessive blood replacement was required that could not be accounted for by external blood loss Paracentesis yielded liquid blood and the child was returned to the operating room A large hemoperitoneum was evacuated and the only source of bleeding was a superficial laceration of the liver presumably caused by subcutaneous tunnelling of a chest tube The child continued to do poorly and died on his first postoperative day The cause of death was a combination of incompletely relieved stenosis of a morphologically primitive mitral valve and intraperitoneal hemorrhage

Two other infants had uncorrectable lesions The child with a heart tumor was found to have a massive rhabdomyoma involving primarily the ventricular septum and occupying much of the left ventricular cavity It partially obstructed the right ventricular outflow tract Left ventricular function was not improved by partial resection of the tumor mass and the child died 8 hours later with biventricular obstruction

The attempt to correct the anomaly preoperatively diagnosed as truncus arteriosus was thwarted by an unexpected finding After resection of a segment of ascending aorta containing the orifices of the pulmonary arteries aortic continuity was re established and the right ventricle was opened Inspection revealed a severe form of complete endocardial cushion defect which precluded total correction

Comment on brain damage

The time of circulatory arrest is limited by potential damage to vital organs The organ that is least tolerant of anoxia and circulatory arrest is the brain An effective modality to prolong the acceptable period of ischemia is hypothermia Despite evidence in experimental animals that periods of up to 2 hours of hypothermic circulatory arrest can be tolerated without neurologic damage, reports of brain damage following deep hypothermia dampened clinical interest in hypothermic circulatory arrest in the early 1960s[8,1] The modifications of technique provided by Horiuchi[11] Hikasa[1] and Mohri[21] and their coworkers in the mid 1960s proved the safety of such procedures in children Their methods have infrequently been associated with postoperative neurologic abnormalities In our series of patients, the three who had seizure episodes were well controlled with medical therapy and none had electroencephalographic abnormalities prior

to discharge The time of circulatory arrest did not seem related to seizures since arrest time ranged from 18 minutes to 50 minutes and longer arrest periods of up to 85 minutes were not associated with seizures

Abnormal neurologic findings have been reported recently in infants undergoing hypothermic circulatory arrest including both seizures and more commonly choreoathetosis It is of interest that neurologic changes are almost always transient We have seen no permanent neurologic damage In one series eight children developed new neurologic findings postoperatively but the abnormality proved persistent in only one child [5] Late follow up of intellectual function in children after hypothermic circulatory arrest has been reported by the Seattle group which has carried out surface induced deep hypothermic operations since 1965 [2] Extensive psychologic testing in patients up to 7 years after operation has demonstrated normal intellectual development in all but a few patients Most of those who were below the range of normal had severe postoperative problems including cardiac arrest and renal failure Thus the early results of long term follow up seem to confirm the safety of this technique

The possibility that a microvascular obstructive lesion *may develop* during the period of hypothermic circulatory arrest has been mentioned by several authors [27, 2] Experimental animals undergoing normothermic circulatory arrest for 5 minutes or *more* develop an obstructive lesion of the cerebral microcirculation [8] Even after circulation is restarted following arrest some areas of the brain are no longer perfused because of this *no reflow lesion* We have demonstrated its occurrence in dogs and rhesus monkeys and have shown that hypothermia (15 to 20 C) protects the cerebral circulation against the development of the *no* reflow lesion *for* periods of up to 2 hours of circulatory arrest [9] It seems unlikely therefore that hypothermic circulatory arrest lasting less than an hour can cause brain damage *through this mechanism* We are continuing these studies however in order to elucidate the mechanisms of brain damage after circulatory arrest during normothermia and hypothermia

Factors other than circulatory arrest are undoubtedly important in producing seizures in these infants For example in our larger series of all infants undergoing hypothermic circulatory arrest nine *developed seizures,* in all but one patient this complication appeared either immediately after a cardiac arrest or a hypotensive episode or during a period of low cardiac output Seizures can be produced by *metabolic factors* such as electrolyte imbalance and hypoglycemia It will be important in the long run to discriminate between the many causes of neurologic dysfunction since only in this way can we assess the contribution of the circulatory arrest method to such disorders and develop ways to provide optimal protection of the brain ischemic injury

Discussion

The place of corrective cardiac surgery in the treatment of congenital heart disease during infancy will ultimately depend upon demonstration of significantly better over all results after early correction than after palliation followed by correction As noted earlier palliative operations produce their own complications that may make later corrective surgery more difficult and dangerous These complications can be avoided by primary correction Psychologic stresses on the patient and family faced with a series of operations during infancy and childhood can be significant [3] The retarded growth patterns often seen in infants with *chronic congestive heart failure or* hypoxia can often be dramatically reversed by corrective operation Though these advantages are real the most compelling arguments in favor *of early correction over staged operations can be* found by comparing the mortality rates of the two methods

VSD This mortality rate for pulmonary artery *banding is inversely related to the age of the* patient In the New England region the mortality rate of infants under the age of 3 months undergoing pulmonary artery banding is 38 6 per cent[3] *Even in patients with isolated VSD* there is a definitely higher mortality rate in children under 3 months of age than in older children [31] Closure of ventricular septal defect and removal *of pulmonary* artery band has been associated with a high mortality rate in some reports [3] but in our last 31 band removals the mortality rate was 3 per cent [33] Others have reported similar *results* [34] The mortality rate of 25 per cent (3 of 12 patients) in our small group of infants under 3 months of age is comparable to the combined mortality rate of banding in the same age group

followed later by corrective operation However, we are not satisfied with these results and believe that better patient selection will improve the mortality rate Young infants with VSD who require surgery and have severe lung disease should have pulmonary artery banding all others should undergo corrective surgery

There is less question about patients over the age of 3 months since there were no deaths in our series of corrective operations in older infants—results similar to those of others[37]

d TGA All patients in this group survived Intraoperative obstruction of the superior vena cava requiring cavopulmonary anastomosis in two infants and late caval obstruction in another have led us to alter our technique of baffle insertion We have found the pantaloon configuration proposed by Brom[38] to be geometrically superior to our previous hour glass shaped baffle and in our last ten consecutive Mustard operations we have seen no evidence of either caval or pulmonary venous obstruction None of these patients has been under the age of 3 months but our experience in older infants has been so satisfactory despite the absence of long term follow up that we plan to use the Brom baffle in smaller babies who require corrective operations

Our previous experience with baffle materials convinced us that there is no particular advantage to either pericardium or prosthetic materials in most children We now use two way stretch Dacron for the baffle and pericardium for enlargement of the functional left atrial chamber We have had no difficulty closing VSD's associated with d TGA through the right atrium in this group of young infants

TOF The mortality rate after shunt procedures for infants under the age of 3 months has been about 50 per cent[39] although this figure may be somewhat lower in recent years[40] Following such palliation the corrective operation with closure of the shunt has had mortality rates of from 8 to 60 per cent[41] Staged operations for patients with tetralogy of Fallot who require surgery in the first 3 months of life therefore result in the death of over half Primary correction has resulted in a dramatic reversal of prognosis for those infants Only one of our seven patients and one of the eight patients of Barratt Boyes' and Neutze[39] under the age of 3 months died Long term follow up evaluation is, of course, not yet available but the mortality rates alone argue very strongly in favor of early correction The requirement in each of our cases for an outflow patch across the pulmonary annulus is a reflection of the severity of anomalies that precipitate an operation during early infancy The short term follow up of our group of patients has been very good, no patient under 3 months of age has required reoperation for a residual lesion Their smooth postoperative recovery stands in sharp contrast to the frequently stormy courses of infants undergoing palliative operations

TAPVC Since there is no suitable palliative operation for TAPVC, correction is the only feasible course in children of any age who have pulmonary hypertension and pulmonary venous obstruction even in the first few days of life The technique of deep hypothermic circulatory arrest has contributed significantly to the improved survival figures that are being reported with increasing frequency[42,43] Because of the relative safety of corrective operation using the new techniques, and because the clinical course of patients with TAVCP is notoriously unpredictable we advise corrective operation for all infants when the diagnosis is made

Miscellaneous lesions Critical aortic stenosis can be approached in many satisfactory ways normothermic total cardiopulmonary bypass, hypothermic circulatory arrest or inflow occlusion without cardiopulmonary bypass[44]

Although successful excision of rhabdomyomas in infancy has been reported,[45] severe cardiac decompensation due to a tumor within the first few days of life carried an extremely grave prognosis The association of this tumor with tuberous sclerosis in 50 per cent of patients makes surgical treatment even less attractive

Despite the fact that the child with truncus arteriosus was inoperable because of an associated complete endocardial cushion defect, the poor results of banding the pulmonary artery in infants who develop intractable congestive heart failure urges an aggressive approach Current techniques for correcting this lesion require the use of a right ventricle to pulmonary artery conduit that will certainly not grow with the patient Despite the inescapably noncurative nature of such an operation during infancy an attempt at early primary correction planning a second procedure to replace the conduit with a larger one in later childhood may be the only hope for survival of most of these patients

Correction of type I truncus arteriosus has been successfully achieved in a 5 week old infant.[3]

Deep hypothermia with circulatory arrest has proved to be an effective adjunct to the surgical therapy of congenital heart disease. We believe that the results of our recent experience justify the application of these techniques during infancy when surgery is required to treat a correctable congenital heart defect.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Electrophysiology and pharmacology of cardiac arrhythmias IX Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade Part B

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Beta adrenergic receptor blockade

The beta adrenergic blocking drugs bind to the beta receptor and thereby prevent the interaction between the catecholamines and receptor which results in the physiological response Because beta receptor blockers *compete* with catecholamines for the binding sites on the beta receptors they are known as competitive blocking drugs A competitive blocking agent is a drug which diminishes or eliminates the physiological effect of a reversible agonist (in this instance catecholamines) by combining *reversibly* with the same receptors as the agonist (Fig 1)

A number of beta receptor blocking drugs are now becoming available for clinical and investigative use These drugs differ in potency specificity (some may block cardiac beta receptors more strongly than the beta receptors of other organs) presence of beta stimulating effects and direct membrane effects which are not related to beta receptor blockade Only one beta receptor blocking drug propranolol currently is approved for use as an antiarrhythmic drug in the United States It has no beta receptor stimulating effects it has direct membrane effects and it may have a more potent blocking action on vasculature and organs other than the heart Practolol is widely used in Europe and to some extent differs from propranolol It has some beta stimulating effects lacks direct membrane effects and may be more of a potent blocker of cardiac beta receptors than of beta receptors in other organs In the following discussion we will concern ourselves mainly with propranolol and practolol although we will mention some of the other agents currently being tested

Antiarrhythmic effects of beta receptor blocking drugs

Although the exact cause of all arrhythmias responsive to beta blocking drugs is not yet known it appears that the sympathetic nervous system can be implicated in the genesis of the majority of them Therefore blockade of sympathetic influences may be the most important mechanism of antiarrhythmic action Unfortunately the use of beta receptor blocking agents in situations where they might be highly effective antiarrhythmics is often precluded by the possibility of development or actual development of undesirable side effects manifested either on the heart (negative inotropic effect depression of sinus rate and atrioventricular conduction) or on *other organs* (hypotension bronchospasm)

Atrial arrhythmias not due to digitalis toxicity Beta receptor blocking drugs often will abolish atrial arrhythmias Persistent sinus tachycardia in children and adults may result from excessive activity in sympathetic nerves due to central nervous system influences increased catecholamine release from nerve endings in the heart or increased catecholamine blood levels (pheochro

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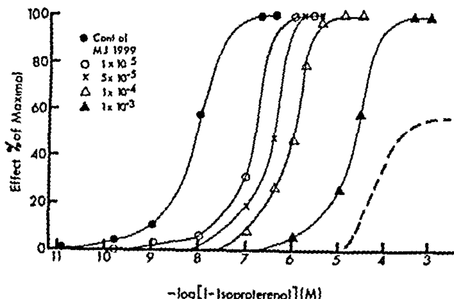


Fig 1 The effect of a competitive blocking agent (*the beta receptor blocker MJ 1999*) on the response of SA nodal rate in the rabbit to increasing concentrations of isoproterenol Change in heart rate is plotted as per cent of maximal effect on the ordinate and the concentration of isoproterenol (negative logarithm of molar concentration) is on the abscissa Solid circles represent values during control exposure of SA node to increasing concentrations of isoproterenol Other solid curves represent values during exposure of SA node to increasing concentrations of isoproterenol in the presence of increasing concentrations of beta blocking drug Note that after beta receptor blockade with each blocking drug concentration a maximum response can still be elicited by isoproterenol although it takes an increased concentration of the agonist to do so This is a major characteristic of competitive blockade which is always reversible increasing the concentration of the agonist results in displacement of the blocking drug from the beta receptor binding site and the occurrence of a physiological response to the agonist Compare this to the dashed curve which is the response which might occur to a noncompetitive blocking drug Now a maximum physiological response cannot be elicited even though a very high concentration of isoproterenol is being used The noncompetitive blocking drug is not displaced from the beta receptor by the isoproterenol (Modified from Strauss H C Bigger J T Jr and Hoffman B F Electrophysiological and beta receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue Circ Res 26 661 1970 Reproduced by permission of The American Heart Association)

mocytoma) Sinus tachycardia also may result from an exaggerated response of the beta receptor to normal levels of sympathetic discharge or catecholamines (hyperthyroidism, thyrotoxicosis hyperdynamic beta adrenergic circulatory state) Undoubtedly there are other causes of sinus tachycardia as well All beta receptor blocking drugs usually slow the sinus rate during sinus tachycardia [1,18]

Although the electrophysiological mechanisms for atrial arrhythmias other than sinus tachycardia are highly variable certain ones can be attributed to either excessive sympathetic activity or reactivity of the heart to sympathetic stimulation Paroxysmal atrial arrhythmias including atrial premature depolarizations paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation may occur in response to exercise or emotion [17,18] Long term propranolol therapy has been highly effective in preventing the paroxysmal atrial arrhythmias in such patients,[17] [1] and presumably other beta receptor blockers should be equally as effective Paroxysmal atrial arrhythmias including paroxysmal supraventricular tachycardia with and without WPW, and paroxysmal atrial fibrillation, which are not exercise induced or obviously related to emotional stress also may be reduced in frequency or abolished by chronic propranolol administration [1,21]

In several clinical studies beta receptor blocking drugs (propranolol alprenolol practolol) have been highly effective in converting to normal sinus rhythm atrial flutter, fibrillation and tachycardia which result from myocardial infarction [4,20]

Beta receptor blocking drugs are usually ineffective in converting cases of nonparoxysmal atrial fibrillation flutter and tachycardia to normal sinus rhythm [3,1,12,14,20,1,7,7] The rate of flutter is rarely altered When atrial flutter or fibrillation is of long duration it is *unlikely to*

result from sympathetic influences on the atrium but rather from pathological alterations in atrial myocardial fibers This may explain the ineffectiveness of beta receptor blocking drugs against these arrhythmias

Atrial arrhythmias resulting from digitalis toxicity The most extensive clinical trials of a beta blocking drug's antiarrhythmic efficacy for digitalis toxicity have been conducted with propranolol Propranolol is particularly effective against both digitalis induced paroxysmal atrial tachycardia with atrioventricular block and atrial premature depolarizations This antiarrhythmic effect may result from removal of a sympathetic component in the genesis of these atrial arrhythmias although one clinical study has indicated a direct membrane antiarrhythmic effect of propranolol Propranolol is not generally used for these arrhythmias because it may significantly depress both sinus rate and AV conduction in this situation

Antiarrhythmic effects on the atrioventricular (AV) node In many instances of atrial fibrillation flutter and tachycardia where beta receptor blocking drugs have failed to abolish the arrhythmias, they still have been successful in slowing the ventricular rate Removal of the tonic sympathetic influences on the AV node by beta receptor blockade slows nodal conduction increases nodal retractoriness and thereby decreases the number of atrial impulses which can conduct to the ventricles

The clinical benefit derived from the use of beta receptor blocking drugs to slow ventricular rate appears to be variable Several reports have indicated that no beneficial hemodynamic effect occurred in patients after propranolol slowed ventricular rate during atrial fibrillation and congestive heart failure has been precipitated by propranolol even when ventricular rate is adequately reduced There also have been cases in which beta receptor blockade with propranolol during rapid atrial rhythms and the resultant slowing of ventricular rate resulted in hemodynamic improvement and even the elimination of congestive heart failure Practolol very rarely worsens the hemodynamic status and usually improves it in patients with these arrhythmias This may be a consequence of the lack of a direct myocardial depressant effect The exact nature of the hemodynamic response to beta receptor blocking drugs during these arrhythmias probably depends on many factors including the degree of slowing of the ventricular rate how sick the heart is and the presence or absence of a direct myocardial depressant effect of the drug

Beta receptor blocking drugs are not the primary agents for slowing the rapid ventricular rate during rapid atrial arrhythmias digitalis is still the agent of choice Nevertheless beta receptor blocking drugs have a very definite and important role They have additive effects with digitalis to increase the AV nodal effective refractory period and therefore can be given in addition to digitalis if digitalis alone does not adequately slow the ventricular rate For example sufficient digitalis cannot be given to some patients with atrial flutter or fibrillation to prevent the increase in ventricular rate which often occurs in response to exercise without the development of digitalis toxicity This increase in ventricular rate may provoke failure and be incapacitating Beta receptor blockade as an adjunct to digitalis may prevent this exercise induced increase in ventricular rate

Since cardioversion causes intense sympathetic activation and since digitalis may enhance the actions of the sympathetic nerves on the heart it is now standard practice to discontinue its administration several days prior to elective cardioversion of atrial fibrillation or flutter Propranolol can be used if needed to prevent a rapid ventricular response to the atrial tachyarrhythmia during the withdrawal of digitalis

Ventricular arrhythmias due to digitalis toxicity A high incidence of success has been achieved in abolishing digitalis induced ventricular ectopic beats and ventricular tachycardia with propranolol or other beta receptor blocking drugs However in the presence of depressed atrioventricular conduction beta receptor blockade may have deleterious effects Incomplete AV block may be converted to complete AV block after ventricular ectopic activity is abolished and the idioventricular rate may be too slow to maintain an adequate cardiac output

Ventricular arrhythmias not due to digitalis toxicity Ventricular premature depolarizations and paroxysmal ventricular tachycardia may be induced by exercise and emotion and may result either from hyperactivity of the sympathetic

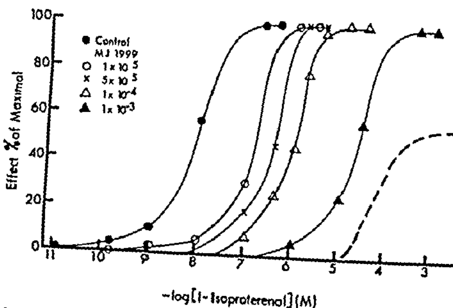


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Clinical pharmacology of propranolol Plasma levels administration and pharmacokinetics

Plasma levels Presumably during propranolol administration a minimum plasma level must be attained so that enough drug can enter the heart to exert its antiarrhythmic effect Ninety to 95 per cent of propranolol in the intravascular compartment is bound to plasma proteins' and measured plasma levels include both the bound and unbound drug Probably only unbound drug can interact with the beta receptors and is pharmacologically active

Although there are few studies available to directly relate plasma levels of propranolol to the antiarrhythmic effects plasma levels which adequately block the effects of the sympathetic nervous system on the electrical activity of the heart will probably be effective against many types of arrhythmias Exact determinations of antiarrhythmic plasma levels are complicated by the presence of propranolol metabolites which also have beta receptor blocking properties but are not detected by the propranolol assay procedures If a significant amount of such a metabolite is present the plasma level of propranolol which inhibits the sympathetic effects might appear to be much lower than if active metabolites were not present The amount of active metabolite present is partly related to route of administration and duration of therapy and therefore variations in antiarrhythmic levels of propranolol may occur as route of therapy is changed and duration increases

Soon after intravenous injection of a single dose of propranolol a situation in which no active metabolites are present in significant concentrations maximal blockade of exercise induced sinus tachycardia (a measurement of sympathetic activity) is achieved with plasma propranolol levels of 100 to 150 ng /ml This level of propranolol also markedly decreases the chronotropic response to isoproterenol After a single oral dose maximum blockade of tachycardia occurs at propranolol plasma levels of about 40 ng /ml due to the presence of significant amounts of the metabolite 4 hydroxypropranolol which is not detected by the assay procedure and which is equipotent in beta blocking activity Presumably arrhythmias due to sympathetic stimulation of the heart would be abolished by plasma propranolol levels in the vicinity of 40 ng /ml soon after a single oral dose and by 100 ng /ml after a single intravenous dose assuming that exercise is a good indicator of maximum sympathetic stimulation

During chronic oral therapy propranolol levels which produce sympathetic blockade are equivalent to the levels needed after acute IV administration (100 to 150 ng /ml) since metabolism of propranolol to 4 hydroxypropranolol seems to diminish with time These or lower plasma levels may be antiarrhythmic during chronic therapy although the presence of other active metabolites may contribute to the antiarrhythmic effect

Propranolol s effectiveness against cardiac arrhythmias which are not obviously related to sympathetic activity may or may not be due to beta receptor blockade Antiarrhythmic plasma propranolol levels have not been reported for digitalis induced arrhythmias arrhythmias associated with acute myocardial infarction or paroxysmal atrial or ventricular arrhythmias We therefore do not know whether the antiarrhythmic drug levels are the same as those needed to block the effects of the sympathetics on the heart However we do know that for treating many of these arrhythmias 10 to 20 mg of propranolol IV has produced a satisfactory antiarrhythmic effect and this dose usually results in initial plasma drug levels of 100 to 150 ng /ml which cause beta receptor blockade In one study plasma propranolol levels of 40 to 85 ng /ml after acute IV administration abolished chronic ventricular premature depolarizations which may have been related to ischemic heart disease Antiarrhythmic effects presumably resulted from beta receptor blockade since the same and much higher levels of d propranolol (which has no beta blocking activity) up to 310 ng /ml had no antiarrhythmic effects

Administration Propranolol can be administered intravenously or orally When given intravenously up to 10 mg (0 1 mg /Kg) is administered at a rate of about 1 mg /min This dose will result in an initial plasma level of about 100 to 200 ng /ml (Fig 2) which is usually adequate to block the effects of the sympathetics on the heart After a single intravenous dose the plasma levels fall off quite rapidly as a biexponential function (Fig 2) There is an early rapid decline ($t_{1/2}$ of about 10 minutes) as the drug enters the tissues followed by a later and slower fall off with a $t_{1/2}$ of two to three hours which is

nervous system or enhanced sensitivity of the beta receptors to catecholamines.[33] Beta receptor blockade is often completely effective in preventing these arrhythmias.[33,1] In patients with the prolonged Q-T interval syndrome, ventricular fibrillation also is related to alterations in sympathetic influences on the heart; fear, anxiety, and startling events may precipitate episodes of fibrillation in these patients.[34] These episodes often cannot be controlled by antiarrhythmic drugs which are devoid of sympatholytic properties. Propranolol has produced the most favorable results in reducing the frequency of syncopal spells in patients with prolonged Q-T interval syndromes even though the Q-T interval remains prolonged after propranolol therapy.[35,3]

Ventricular arrhythmias may also result from sympathetic nervous stimulation of the heart during anesthesia with halothane or cyclopropane; these anesthetics sensitize Purkinje fibers to the automaticity-inducing effect of catecholamines.[37] Beta receptor blocking drugs are effective in preventing or abolishing these arrhythmias.

Propranolol and other beta receptor blocking drugs have only been partially effective in suppressing chronic ventricular premature contractions of unspecified etiology, and mostly ineffective in converting chronic ventricular tachycardia to sinus rhythm.[1,4]

Ventricular arrhythmias due to ischemic heart disease and myocardial infarction. The mechanisms for arrhythmias associated with infarction might vary depending on the extent of tissue damage and the time after coronary occlusion.[38] The sympathetic nervous system seems to be of particular importance in the genesis of the early arrhythmias which occur within minutes to hours after a coronary occlusion. Arrhythmias which occur several days after coronary occlusion or chronic arrhythmias which persist after infarction may or may not have a significant sympathetic component. Beta receptor blockade may only have significant antiarrhythmic effects during arrhythmias resulting, at least in part, from sympathetic activity.

Clinical trials have evaluated the efficacy of chronic propranolol administered for the prevention of sudden death due to myocardial infarction arrhythmias. These trials have shown no significant reduction in mortality.[39,40] However, these results should not be taken as final evidence that beta receptor blocking drugs do not decrease the incidence of arrhythmias which may cause sudden death. The possibility exists that in many patients on chronic oral therapy beta receptor blockade is not adequate and this should be considered in future trials of prophylactic therapy.

Beta receptor blocking drugs such as propranolol, alprenolol and practolol when given intravenously in the coronary care unit for acute ventricular arrhythmias after myocardial infarction have been effective in abolishing ventricular premature contractions and paroxysmal ventricular tachycardias.[4-41] These drugs are not as effective against sustained ventricular tachycardia. The effectiveness of practolol, which has no direct membrane effects, indicates the importance of beta receptor blockade as an antiarrhythmic intervention.[1] These drugs are not used extensively at this time mainly because of possible adverse hemodynamic effects. Although Lemberg and associates[4] consistently found improvement in hemodynamics due to conversion of rapid arrhythmias and the slower resultant cardiac rate, this has not been the experience of others.

Combined use of beta receptor blocking drugs with other antiarrhythmic agents. The combination of propranolol and quinidine has sometimes been more effective than quinidine alone in preventing the return of atrial fibrillation after DC cardioversion.[4,5] Propranolol and quinidine and propranolol and procaine amide also have been administered for ventricular arrhythmias which were resistant to either quinidine or procaine amide alone.[42] These arrhythmias may result, at least partly, from sympathetic influences on the heart which cannot be prevented by antiarrhythmic drugs devoid of beta receptor blocking properties. Antiarrhythmic action also may be due to synergistic direct membrane effects.

Arrhythmias due to cardiac effects of pharmacologic agents. The tricyclic antidepressants occasionally may cause palpitations, chest pain and cardiac arrhythmias by activating the sympathetics to the heart. These effects may be successfully prevented by beta receptor blockade. The cardiac arrhythmias which sometimes result from beta receptor stimulation during levodopa administration also are prevented by propranolol.[43]

in enhanced further metabolism of 4 hydroxypropranolol or there may be an alternative primary metabolic pathway for propranolol

4 hydroxypropranolol has significant pharmacologic effects It is a beta receptor blocker with a potency similar to propranolol it has some sympathomimetic effects and also direct membrane actions[3] It therefore may contribute to the antiarrhythmic effect of propranolol when it is present in the plasma in significant amounts

Many other propranolol metabolites have been identified in both blood and urine of animals and man (Fig 3) One or more of these metabolites may contribute to the pharmacological effects of propranolol For example α naphthol has acute effects on heart rate arterial pressure and myocardial contractility[50] Isopropylamine increases arterial pressure heart rate and myocardial contractile force[6] Propranolol glycol has potent anticonvulsant effects Detailed studies on the possible antiarrhythmic potencies of these metabolites have not yet been accomplished

The rate of propranolol metabolism is not linearly related to plasma propranolol levels and the metabolic enzyme system is capacity limited During the course of chronic oral therapy with propranolol the $t_{1/2}$ for elimination (which is almost entirely a measurement of the rate of metabolism) may gradually increase by close to 50 per cent[3] The change in $t_{1/2}$ presumably occurs because metabolism is dose dependent and the enzyme system responsible for metabolism becomes saturated in much the same manner as diphenylhydantoin The $t_{1/2}$ begins to prolong with oral doses greater than 40 mg every six hours (nonlinearity in the dose/plasma ratio may occur when plasma levels of 70 ng/ml are reached) Dosage or plasma levels at which the enzyme system is completely saturated and elimination occurs with zero order kinetics are not known

Factors influencing propranolol plasma levels

Significant variations in the degree of plasma protein binding are often found between individuals and these variations can affect the rate of propranolol metabolism For many drugs metabolism is restricted to the free drug in the circulation but not for propranolol bound drug is metabolized as well as the free drug Binding of propranolol to blood proteins accelerates its metabolism by delivering more drug to its site of inactivation Individuals with a greater degree of

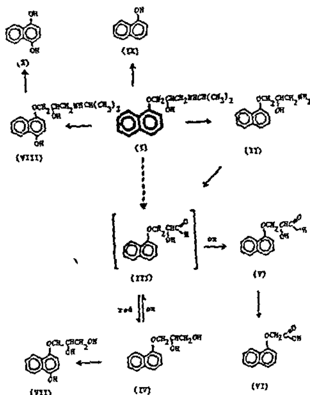


Fig 3 Schematic representation of propranolol metabolism in man and dog The parent compound propranolol (I) is metabolized to a number of metabolic products which include (II) N-desisopropylpranolol (III) proposed aldehyde (IV) glycol (V) 3-(α naphthoxy) lactic acid (VI) α naphthoxyacetic acid (VII) OH glycol (VIII) 4 hydroxypropranolol (IX) α naphthol (X) dihydroxynaphthalene (Reproduced from Walle T and Gaffney T E Propranolol metabolism in man and dog Mass spectrometric identification of six new metabolites J Pharmacol Exp Ther 182 83 1972 Reproduced by permission)

plasma protein binding have a shorter $t_{1/2}$ for elimination indicating the more rapid metabolic disposition of the drug The degree of protein binding also affects the rate of elimination by altering the volume of distribution Increased plasma binding decreases the volume of distribution and tends to shorten drug half life

Hepatic blood flow determines the rate of delivery of propranolol to the liver and factors which alter hepatic blood flow markedly affect the rate of drug metabolism Propranolol limits its own metabolism since it decreases hepatic blood flow by its beta receptor blocking effect[6] Reduced hepatic blood flow by congestive heart failure also may be expected to decrease the rate of propranolol metabolism Liver disease may

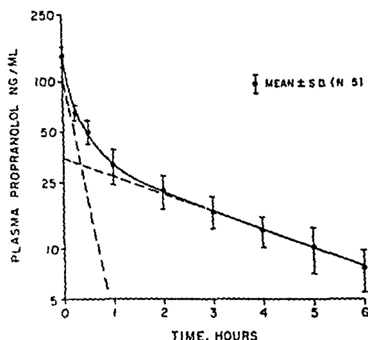


Fig 2 Plasma propranolol levels after a 10 mg intravenous infusion at a rate of 1 03 mg /min Each point represents the mean and standard deviation of the levels determined in five subjects The late exponential phase has been extrapolated to zero time and the early exponential phase defined by the calculation of residuals (Reproduced from Shand D G Nuckolls J M and Oates J A Plasma propranolol levels in adults Clin Pharmacol Ther 11 112 1970 Reproduced by permission)

mostly due to metabolism [1] A single intravenous dose of 10 mg which produces a plasma level of 150 ng /ml may therefore decline to below 50 ng / ml within one hour The sympathetic blocking effect falls off with the decline in plasma level The antiarrhythmic effect of a single intravenous dose of propranolol usually lasts for several hours Maintenance of therapeutic plasma or tissue levels subsequent to IV propranolol administration usually is accomplished by oral administration

When propranolol is administered orally a remarkable variability in plasma levels can occur between different patients even when they are given the same doses and complete absorption from the intestine occurs In five patients studied by Shand and associates[53] plasma propranolol levels varied by 7 fold (30 to 210 ng /ml) after oral administration of 80 mg This makes prediction of an exact oral dosage schedule difficult A large quantity of the initial oral dose of propranolol is immediately extracted from the portal circulation by the liver [11] This is due not only to metabolism but also results from high affinity liver binding sites [54] Individual differences in hepatic extraction may be at least partly responsible for the differences in plasma level [55] Unusually low plasma levels of propranolol might therefore occur in certain individuals resulting in ineffective antiarrhythmic action Usually if the initial dose of oral propranolol is less than 30 mg none of the drug may reach the systemic circulation due to almost complete hepatic extraction [54, 55] An increase in the initial oral dose above 30 mg results in an increase in plasma levels because more drug passes through the liver without being removed from the circulation The high affinity liver binding sites are saturated by initial doses of approximately 30 mg or more and remain saturated for up to six hours thereafter [5] Therefore a larger amount of drug reaches the systemic circulation after subsequent oral doses during the first pass of the portal blood through the liver

During chronic propranolol therapy the intervals between oral doses should maintain plasma or tissue levels within the therapeutic range Since the $t^{1/2}$ for elimination of propranolol during chronic oral therapy may range from three to six hours[11] oral propranolol is usually administered every six hours to accomplish this objective

Metabolism Almost 95 per cent of propranolol in the body is metabolized and very little is excreted unaltered in the urine [11, 58] Most of the metabolism occurs in the liver but there is some evidence that propranolol may be metabolized in the lung as well [57, 5]

Propranolol undergoes a number of degradative reactions leading to a wide variety of metabolites After an initial oral dose large quantities of 4 hydroxypropranolol are formed by the liver [4, 49, 4] The quantity of 4 hydroxypropranolol formed after an initial IV dose is not nearly as great Apparently a high concentration of propranolol is required in the portal venous blood (as occurs after oral administration) in order for the drug to be metabolized to significant quantities of 4 hydroxypropranolol [49, 58] The plasma levels of 4 hydroxypropranolol are only significant during the first few hours after an oral dose and are insignificant by six hours after administration, suggesting that it is further metabolized with a shorter $t^{1/2}$ than propranolol [4] 4 hydroxypropranolol does not appear to be a major end metabolic product during periods of chronic drug administration plasma levels are undetectable after five days of continuous propranolol administration [49] Self induction of enzymes might result

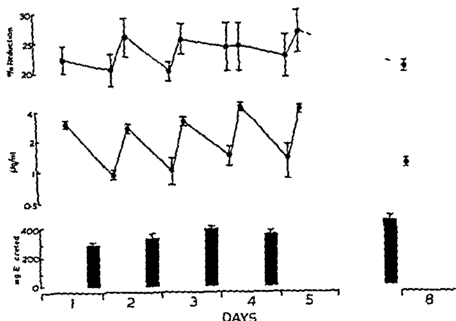


Fig 5 The mean percentage reductions of exercise heart rate (± S E M) and the corresponding mean blood practolol levels before and two hours after a daily oral dosage of 400 mg practolol for one week After two days plasma levels do not fall below 1 µg/ml The mean daily urinary excretion of practolol is shown by the solid vertical bars and accounts for almost the total amount of administered drug (Reproduced from Carruthers S G Kelly J G McDevitt D G and Shanks R G Blood levels of practolol after oral and parenteral administration and their relationship to exercise heart rate, Clin Pharmacol Ther 15 43, 1973 Reproduced by permission)

time plasma levels are maintained at 1 µg/ml after 80 mg and 0 5 µg/ml after 40 mg The degree of beta receptor blockade produced by these different plasma levels as judged by the effects on exercise induced heart rate increase over this six hour period is not significantly different Plasma levels then begin to decline the t½ for elimination is between 10 and 13 hours After doses of both 80 and 40 mg significant beta receptor blockade is still evident at the end of 24 hours although at this time the initial 80 mg dose has a greater effect (Fig 4) After initial intravenous administration maintenance therapy usually is provided by subsequent oral administration

After oral administration practolol is rapidly and completely absorbed from the intestines and significant blood levels begin to appear within 15 minutes in the fasting individual There is less than a twofold variation in plasma levels between individual subjects given the same dosages in contrast to the wide variability in plasma propranolol levels One hundred mg of practolol usually produces plasma levels of about 1 5 µg/ml and maximal blockade of exercise induced tachycardia so higher oral doses are probably unnecessary to achieve an antiarrhythmic effect Four hundred mg orally produces plasma levels of about 3 0 µg/ml and maximum blockade may be maintained for 24 hours during which time plasma practolol levels don t fall below 1 µg/ml (Fig 5) Comparable effects can be obtained with 200 mg every 12 hours

Inactivation Practolol is not metabolized in humans Renal excretion is the only means whereby the pharmacologic effects are terminated (Fig 5) The drug is filtered by the glomeruli and not reabsorbed in the tubules Excretion is therefore not affected by variations in urinary pH between 5 2 and 8 0 Presumably any alterations in glomerular filtration such as those which occur during congestive heart failure or renal disease will cause practolol to accumulate during chronic administration

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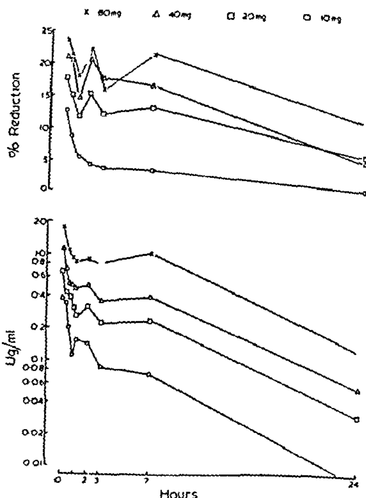


Fig 4 The effects and blood levels of practolol after single intravenous doses Mean values for 80 mg (n = 3) 40 mg (n = 3) 20 mg (n = 6) and 10 mg (n = 3) are indicated (n = number of patients) At the top the percent reduction in exercise induced tachycardia for each dose is shown Maximum reduction is approximately 25 per cent At the bottom practolol blood levels at the time of administration until 24 hours later are indicated (Reproduced from Carruthers S G Kelly J G McDevitt D G and Shanks R G Blood levels of practolol after oral and parenteral administration and their relationship to exercise heart rate Clin Pharmacol Ther 15 497 1973 Reproduced by permission

also retard the rate of propranolol metabolism All these factors will increase propranolol plasma levels

Higher propranolol levels are found in patients with chronic renal disease as compared to patients without renal disease after an initial oral dose [8] even though propranolol is not normally excreted by the kidneys Chronic renal disease may result in an increase in propranolol plasma levels by decreasing hepatic tissue binding the mechanism is unknown As a result hepatic extraction of propranolol during the first pass through the liver after an initial oral dose is decreased and the fraction of this oral dose available to circulate and exert its phamacologic effects is increased The reduced hepatic binding may not influence the rate of drug metabolism once the functional binding sites are saturated or the decrease in volume of distribution which occurs in patients with renal disease may eventually offset any decrease in liver metabolic rate [9] Therefore when beginning therapy in chronic renal insufficiency it may be necessary to give smaller propranolol doses initially and the doses can then be gradually increased Although during chronic administration high daily doses of propranolol may be well tolerated by patients with kidney disease [68] metabolic products of propranolol may accumulate in the blood and exert phamacological effects that influence the outcome of therapy This has not been investigated

Clinical pharmacology of practolol plasma levels administration and pharmacokinetics

Plasma levels Since practolol does not have significant direct membrane actions[6] and is not metabolized [61] the antiarrhythmic effects must result from its beta receptor blocking action Plasma levels necessary for the maximum inhibition of exercise induced tachycardia show individual variability and range from 1 0 to 2 5 µg/ml [69 70] Plasma levels for beta receptor blockade do not vary depending on the route of administration as shown for propranolol [5] Because practolol is bound to protein to only a minor degree these measurements of plasma levels indicate free drug

Administration Practolol can be administered intravenously orally or intramuscularly although the latter route is rarely used When given intravenously to patients with normal renal function, a total dose of 20 mg produces initial plasma levels of 0 5 to 1 0 µg/ml (Fig 4) and although this may not be sufficiently high to maximally block exercise induced tachycardia these plasma levels may still have sufficient beta receptor blocking actions to exert an antiarrhythmic effect Forty mg produces initial plasma levels of 1 0 to 1 5 µg/ml and 80 mg produces plasma levels of about 2 0 µg/ml which maximally block exercise induced tachycardia [6] After administration of a single IV dose blood levels fall off rapidly during the first hour due to some drug movement into the tissues and then may remain relatively constant over the next six hours or may even increase slightly due to enterohepatic recirculation of practolol (Fig 4) Over this period of

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change or plain myth and this would be most undesirable For no one who has watched the arteries on the surface of the brain contract locally to the point of obliteration against maximal rises in blood pressure can doubt the ability of these vessels to cause cerebral ischemia in appropriate circum stances and such ischemia would presumably have to be called angiospastic

But, in an organ which is exquisitely sensitive to lack of oxygen it is ischemia and not semantic hair splitting that matters Neurology has never lacked unsolved mysteries and it is not hard to think of examples which may well be ischemic in origin Puerperal psychosis, for instance stands apart from mental illness in general. It occurs at a time when secretion levels of estrogens progesterone and oxytocin have all been changing and it may be more than a coincidence that physio logic doses of the two steroids can augment the vasocon strictor effect of oxytocin as much as seventy fold A more common example is the ubiquitous migraine which carries more than a hint of arterial caliber changes and may yet be found to be nothing more mysterious than a sudden over taxing of autoregulation of blood flow

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Pacemaker nonsense

Pacemaker induced ventricular tachycardia or fibrillation is occasionally encountered as a complication of fixed rate car diac pacing This is, indeed, the rationale and justification for use of ventricular demand pacing However a properly func tioning demand pacemaker may induce ventricular fibrillation by firing inappropriately during the vulnerable period of ventricular repolarization Such a case is reported below

An elderly male was transferred to Thomas Jefferson University Hospital for treatment of an acute anterior wall myocardial infarction. At the time of admission a twelve lead electrocardiogram confirmed the presence of an acute current of injury Complete atrioventricular dissociation was present with an idioventricular rhythm of 5? beats per minute A bipolar pacing electrode was positioned in the right ventricle and ventricular capture was satisfactorily performed with a Medtronic demand pacemaker (Model 5880) at low amperage (< 3 ma) During a sequence of turning the pacemaker generator off and on the unit was inadvertently activated during the vulnerable period of ventricular recovery (Fig 1) Ventricular fibrillation ensued and was terminated by external countershock therapy Proper pacing was subse

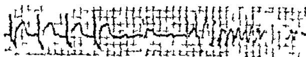


Fig 1 Atrioventricular dissociation After four paced beats the pacemaker is inactivated. This is followed by two idioven tricular beats, the repolarization of the second being inter rupted by reactivation of the demand unit Ventricular fibril lation follows.

quently resumed. In spite of pacing and various measures for pump failure the patient developed a shock syndrome and died

Demand ventricular pacing depends upon generator inhibi tion by the intrinsic ventricular depolarization potential. This negative feedback mechanism occurs once the unit has been turned on. However it is nonfunctional at the time that the pacemaker generator is initially activated Turning the switch "on" immediately discharges an impulse Thus, a properly functioning demand unit performs as a fixed rate pacemaker for the first beat. Theoretically this impulse is

Annotations

Spasm, constriction, and hypertensive cerebral arteries

Twenty years ago the century old controversy about the cerebral blood flow in the acute crises of hypertensive disease seemed to have been settled by the demonstration of intense focal constriction of the cerebral arteries in the hypertensive rats with acute encephalopathy [1] a finding later confirmed in cats dogs and monkeys with severe hypertension Since this early observation however it has become increasingly difficult to accept the original conclusion that the observed constriction even when virtually obliterative was pathologic spasm responsible for the accompanying pallor focal edema and arterial necrosis by causing ischemia For instance serial photographs of the retinal[3] and cerebral arteries during the evolution of chronic hypertension—a matter of weeks or months in the Goldblatt rat—showed that the constriction develops very gradually after the blood pressure has reached a high level and is often fully developed for weeks before the slightest evidence of cerebral abnormality can be detected [4] Moreover the constriction can be made to disappear and reappear promptly smoothly and predictably if the blood pressure is made to fall and rise for instance by varying the level of ether anesthesia which has a rapidly reversible depressor effect in renal hypertension (Figs 1 A and 1 B)

This is a very different picture from the sudden cramp like contraction which is usually implied by the term spasm and clearly points to a chronic accurately controlled constriction Its true nature is revealed by the fact that zones of constriction are separated by less conspicuous zones of dilation which also respond reciprocally to changes in pressure If it is assumed that arterial muscle is not evenly distributed it follows from simple physical laws that a blood pressure which rises high or quickly enough to outstrip normal reserves of tone and muscular hypertrophy will produce a critical situation at which weaker zones will dilate and in doing so become even weaker at a time when stronger zones can still contract and become even stronger and better able to offset the dilation and maintain normal blood flow [5]

The link between this complex pattern and encephalopathy is supplied by three observations First sudden overstretching of an artery has been shown to cause focal necrosis of its wall the essential structural lesion of encephalopathy and of malignant hypertension second the pattern of constriction and dilation as seen in the intestinal arteries of the rat[7] can be exactly duplicated by injecting angiotensin[8] and third in such animals fluid can be seen to leak into and through the arterial wall *always in zones of dilation* as soon as the pressor response to angiotensin reaches its peak [10]

This last demonstration by Giese of primary leakage from over stretched segments of arteries—as distinct from secondary nonspecific leakage into previously damaged arteries—is crucial to an understanding of encephalopathy for scattered leaks of this kind into the grey matter of the cerebral cortex offer a simple explanation of all the features of this complication of acute hypertensive arterial disease without necessarily invoking any change in cerebral blood flow in either direction [11]

Nevertheless great interest in cerebral blood flow has been



Fig 1 Reversible change in caliber in a cerebral artery in a rat with severe uncomplicated hypertension as seen through a permanent cranial window × 16 A systolic blood pressure 235 mm Hg A large branch of the middle cerebral artery is almost completely closed B seven minutes later blood pressure 165 mm Hg The occluded zone is now well dilated (From Byrom F B The hypertensive vascular crisis an experimental study London 1969 William Heinemann Ltd p 43 Reproduced by permission)

re awakened by the finding that angiotensin infused at carefully controlled rates into normal and hypertensive subjects causes a sudden increase in flow and it is widely suspected that a similar breakthrough of autoregulation may underlie encephalopathy Direct evidence on this point is difficult to obtain but the fact that cerebral edema in spontaneous crises in hypertensive rats is very focal in origin suggests that any increase in flow is likely to be equally focal It is perhaps relevant also that zones of constriction in the cerebral arteries have never been seen by the present writer to give way before rising tension even after months of observation

But whether or not these recent studies bear fruit there is a real danger that in recoiling from the emotive word spasm the student will tend to brush aside the clearly demonstrated focal constriction as optical illusion artifact species specific

find significant studies on the intra arterial use of protamine

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Of classification of cardiomyopathies

Cardiomyopathies, just as any group of diseases should be classified for the convenience of the clinician for communication diagnosis, management and study However for the convenience of clinicians the classification must be simple and practical. Classification of cardiomyopathies should stimulate the physician to consider immediately the etiology prevention, and early recognition of the disease This type of classification imposes no restrictions on diagnosis and care When disease of the myocardium reaches the late stages such as marked cardiomegaly and congestive heart failure the disease is at a terminal state and usually at an irreversible state Furthermore the late states are readily recognized by the clinician but the prognosis is extremely grave then It is when patients are in those final stages of their disease that they are usually referred to the cardiologist for management. Thus, a cardiologist who practices little or no internal medicine has little opportunity to see the initial and early stages of cardiomyopathies, i. e., when the disease is preventable and cure is most possible Thus, it is the general practitioner general internist or physician or family doctor who will have the opportunity to detect in patients the presence of etiologic factors that are potential producers of myocardial disease It is the family physician who has the opportunity to detect the diseases early As indicated many years ago infections, anemia, toxins, and many other factors can damage the myocardium These etiologic factors must be avoided or at least detected early and removed. When the myocardial damage is already present, it must be recognized early so that treatment can be instituted early long before his illness progresses into congestive heart failure or any final irreversible state Therefore the average cardiologist does not seem to be prepared or have the opportunity to prevent cure or significantly ameliorate heart muscle disease Nevertheless, he must be concerned with prevention and early treatment The physician must recognize the existence of factors which can damage the myocardium and remove those potential etiologic factors.

Fortunately the presence of etiologic factors and the initial early stages of the cardiomyopathies are readily recognized by a simple clinical work up" i. e., without the use of cardiac catheterization cardioangiography or other complex and unnecessary and hazardous procedures and even before these complex procedures can reveal abnormalities It must be remembered, however that idiopathic hypertrophic subaortic stenosis can offer diagnostic difficulties especially in extremely early diagnosis Fortunately this entity is rare so that it is an extremely insignificant problem in the practice of the average family physician, whereas many of the other cardiomyopathies are common These can and should be recognized early The factors known to produce cardiomyopathy are readily detected so that they can be removed. This practice in turn treats or eliminates "potential" cardiomyopathy

Finally if prevention and cure are the objectives in the management of the cardiomyopathies, then an understanding of etiology pathogenesis potential disease and initial and early myocardial damage must be emphasized in training and in practice It is for this reason that the classification previously published by us was developed All diseases have a cause and a beginning and every possible effort must be exercised at all times and continuously to learn the cause of cardiomyopathy so that the myocardial disease can be prevented or detected and managed in its incipiency

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subject to the disadvantages of fixed rate pacing The above case illustrates that this is more than of theoretical importance

Ventricular fibrillation due to pacemaker stimulus "R on T" phenomenon has occurred during acute myocardial infarction[3] during treatment with catecholamines and shortly after pacemaker insertion[4] At these times and probably at all times activation of demand temporary pacemakers should be performed in the following manner Initially milliamperage should be at the nadir Second the unit should be switched on at a time other than the vulnerable interval Last the milliamperage should be increased until proper capture ensues These steps practiced routinely will minimize such complications of pacemaker therapy

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Protamine-renografin chemical embolus

There have been several recent reviews of complications of coronary arteriography using the transfemoral approach Several authors including Walker and co workers Judkins and Gander and an annotation by Eyer have noted the significant decrease in thromboembolic complications following the use of heparin prior to the initiation of arteriography McCarty and Glasser have also reported on the thrombogenicity of guidewires in the experimental animal They also noted that heparinization seemed to decrease the tendency toward clot formation It is of interest that Walker and co workers[1] and Eyer[2] both use protamine at the conclusion of a catheterization No complications have been reported with the use of protamine as a coagulant drug in coronary arteriography Jaques reported in the *Canadian Medical Association Journal* on a review of protamine The toxicity of protamine has not been promulgated extensively He notes significantly that protamine when injected rapidly will release histamine and agglutinate platelets Protamine can when introduced intravenously cause a pronounced fall in blood pressure in most animal species Most of the actions are thought to be histamine like in nature These effects seem to be reduced by injecting the protamine slowly Protamine combining with heparin in the mast cells will displace histamine and/or serotonin Protamine first combines with exogenous heparin in the circulation and only when there is protamine in excess of the amount required for combination of the mast cells affected Gourin Stresian and Stuckey[4] have observed adverse effects on the electrocardiogram related to histamine release This is probably a further reason for limiting the protamine dosage to that equivalent to heparin in the circulation Ellison Ominsky and Wollman reported that intravenous injections of multiple doses of protamine in eight volunteer subjects totaling 800 mg per 70 kilograms produced typical symptoms of histamine release i e itching flushing fatigue malaise nausea vomiting headache hyperventilation and temperature elevation All of the subjects exhibited itching flushing and only one subject showed hyperventilation and temperature elevation The intensity of these symptoms increased as the dose was increased When titration is not done it is best to depend on the rule of thumb that not more than 1 mg per 100 USP units of heparin be given for neutralization The amount should be reduced in proportion to the time which has elapsed since the last heparin administration by about 1 mg per minute for the average patient.[3]

A second complicating feature is the effect of protamine on Renografin 76 (meglumine diatrizoate) Most videopatent dyes have a basic base Renografin 76 has a pH of 7 0 to 7 6 As is common with transfemoral arteriography frequent flushing is the rule If at the conclusion of the catheterization the protamine is given intra arterially and the dye is withdrawn in the syringe the dye if not flushed out of the catheter will then be withdrawn into the syringe with prompt clumping and a white precipitate being formed within the syringe containing the protamine Protamine sulfate has a pH of 3 to 4 which will cause precipitation of diatrizoic acid

It is conceivable that if this precipitate is then injected intra arterially a significant chemical embolus may result It is therefore the purpose of this brief annotation to caution the arteriographer to be certain that his catheter is free of any radio-opaque contrast media before the injection of protamine The drug may be given intravenously without difficulty hopefully The side effects as noted previously must be watched for There does not appear to be any precaution against the intra arterial use and I have not been able to

Book reviews

Studies in Preventive Cardiology By Daniel Brunner M D F A C C Jaffo Israel 1973 Tel Aviv University

Brunner has produced a book on an aspect of cardiology which is not only most important but often neglected in the whirlwind of therapeutic cardiology The book is divided into nine chapters which are concerned with epidemiology of coronary risk factors, physical activity and the heart nutrition and lipoproteins and other aspects of preventive and rehabilitative cardiology The presentation is not only lucid but presents in a very well condensed manner the extensive literature on cholesterol metabolism and lipoprotein factors in atherosclerosis. The problems of exercise and rehabilitation are also clearly and succinctly presented This book is based to a large extent upon the studies of Brunner and his associates Current interests in cardiology make this a valuable book to study and own. It is highly recommended

Cardiovascular Nuclear Medicine Edited by H William Strauss, M D Bertram Pitt M D and A Everette James Jr M D St Louis 1974 The C V Mosby Company 383 pages. Price $39 50

The editors and contributors of this book discuss the general aspects of nuclear medicine as applied to cardiovascular diseases. The presentations include instrumentation radiopharmaceuticals image display systems clinical applications and radioimmunoassay of cardiac glycosides The presentations are brief but practical. The physician will find this book to be useful, whereas researchers will find it too brief The book does clearly indicate the application of nuclear medicine in cardiology Every physician will find this book to be useful since the role of nuclides is important in the practice of medicine today

Valvular Heart Disease Edited by Edmund H Sonnenblick, M.D and Michael Lesch, M D New York 1974 Grune & Stratton Inc. 400 pages.

This publication is a single bound duplication of the papers which appeared previously in *Progress in Cardiovascular Diseases* The book contains contributions from many individuals involved in medical management and surgical care of patients with valvular heart disease The presentations are concerned primarily with the present state of knowledge and considerations of management of valvular heart disease This book, therefore is not intended for undergraduate medical students who are learning the fundamental physiologic and clinical manifestations of valvular disease Residents interns and interns will find this review valuable The discussions of radiologic manifestations the click syndrome of mitral valve prolapse the preoperative care of patients undergoing heart valve surgery and the results of surgery should be of special interest. This is a valuable publication about an important aspect of cardiology

Pathologie Vasculaire 3 Pathologie Lymphatique By Marceau Servelle Paris 1975 Masson & Cie Editeurs 327 pages

This third volume on vascular pathology is concerned with pathology of the lymphatics Servelle has produced an important book on a subject which is too frequently neglected in medicine The chapters include discussions of elephantiasis chyle and pathology of the thoracic duct lymphatics of the heart lungs liver intestinal tract and other organ systems Methods for visualizing the lymphatics are also described The anatomy of the lymphatics and lymph drainage from various organs is well illustrated This is an excellent book which should be translated into English and probably will be It is highly recommended for physicians who can read French

Synthetic Fibrinolytic Thrombolytic Agents Chemical Biochemical Pharmacological and Clinical Aspects Edited by K. N von Kaulla M D and J F Davidson M D Springfield Ill 1975 Charles C Thomas, Publisher 489 pages

This book contains excellent review articles of fibrinolytic and thrombolytic agents. It represents the proceedings of an international symposium held in Paris in September 1972 The contributors experts in their respective fields reviewed the problems of blood clotting thrombosis and agents which might lyse thrombi in situ The problem of thrombosis and emboli is a most important one in clinical practice Physicians will find this publication to be a bit complex but hematologists and physiologists should profit more from the publication The organization and presentation of this book is similar to that of all proceedings. This is a very good review of the subject and is still timely and up to-date

Cardiovascular Drug Therapy Edited by Kenneth L. Melmon M D Philadelphia 1974 F A Davis Company 284 pp Price $18 75

This is another practical clinical issue of Cardiovascular Clinics. Melmon and his associate contributors summarize the common drugs used in cardiology These include anticoagulants, lidocaine digitalis antihypertensive agents, vasodilators, propranolol and others As a reader would expect these contributors review the indication pharmacology use contraindications unfavorable reactions and other aspects of these drugs. The discussions are directed at the practicing physician There are other important drugs used in cardiology which are not emphasized or included such as antibiotics sedatives, hypnotics parasympathetic nervous system inhibitors, laxatives, and minor but still important drugs in the practice of medicine Nevertheless this is a good and useful publication

Letters to the Editor

First and second heart sounds

To the Editor

I read with interest the excellent paper entitled Changing views on the mechanism of the first and second heart sounds by Dr A A Luisada and colleagues, which appeared in THE JOURNAL (Vol 88 503 514 1974)

I just would like to bring to your attention that although the material was excellent however some errors have occurred

1 There are 62 references at the end of the paper whereas I could find only 60 references in the text

2 A serious error has occurred on page 512 second column "An article published during the preparation of this manuscript" " in which Dr Luisada tries to disprove his own claims, because the first author of reference 59 is Dr Luisada himself

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Reply

To the Editor

I wish to thank Dr Shakibi for calling attention to two errors in the references which were caused by the several revisions of the manuscript

The reference cited on page 512 should have been 61 instead of 59 Reference 62 should have been added to reference 56 on page 510

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A complication of cardiac resuscitation

To the Editor

We read with considerable interest the letter of Drs Atcheson and Fred on complications of cardiac resuscitation (AM HEART J 89 263 1975) We should like to draw attention to another possible complication compression fracture of the spine It is surprising that little reference is made of this finding in the literature and it is very possible that it is being overlooked Okel reported a single case of vertebral fracture which he felt was related to numerous (35) high energy countershocks administered during a successful resuscitation effort The possible cause in this instance was felt to be the generalized muscle contractions produced by the counter shock A compression fracture has also been reported following convulsions in the carotid sinus syndrome[2] These two reports would suggest a mechanism similar to that observed in psychiatric patients undergoing elective counter shock

Perhaps this problem is being overlooked and suggests the need for thoracic and lumbar spine films in all patients who have been successfully resuscitated It is strange indeed that this finding is so infrequently observed when one considers the incidence of osteoporosis as well as the frequently vigorous closed-chest massage and repeated countershocks that are a daily occurrence in our general hospitals.

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The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year

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Books received

Size at Birth CIBA Foundation Symposium No 27 Amsterdam Holland 1974 Elsevier Scientific Publishers 197 pp

Pathophysiology of Blood By Allan J Erslev M D and Thomas G Gabuzda M D Philadelphia 1975 W B Saunders Company 175 pp

Cerebral Angiomas Advances in Diagnosis and Therapy Edited by H W Pia J R W Gleave E Grote and J Zierski New York 1975 Springer Verlag 281 pp Price $23 80

Engineering in Medicine By Dr B McA Sayers Dr S Swanson and Dr B W Watson New York 1975 Oxford University Press 99 pp Price $11 95

Services for Cardiovascular Emergencies World Health Organization Geneva 1975 126 pp Price 10 Swiss francs.

Le Stethoscope Vasculaire a Ultra Sous By Docteur René Milleret, Lyon France 1974 Edipnm 77 pp

Annual Review of Medicine Selected Topics in the Clinical Sciences Edited by William P Creger C H Coggins, and E W Hancock Palo Alto Calif 1975 598 Annual Reviews, Inc 598 pp

***Normal Conduction System and the Electrocardiogram* Programmed Instruction Unit** By Nancy Fairchild Clark, R.N Philadelphia 1975 F A Davis Company 96 pp Price $3 95

Announcements

Pediatric and adolescent echocardiography course

The Department of Pediatrics University of Arizona will present a didactic and practical course in one and two dimensional pediatric echocardiography November 14 to 16 1975 The meeting is timed to just precede the American Heart Association meetings in Anaheim Two types of registration are available (1) Didactic only (2) Didactic plus 9 hours experience with one and two-dimensional instrument systems. Course faculty include S J Goldberg M D H D Allen M D D J Sahn M D W L. Henry M D J M Griffith M S E E and R Solinger M D

For further information contact S J Goldberg Department of Pediatrics, University of Arizona School of Medicine Tucson Ariz. 85724

Jane Nugent Cochems competition

The University of Colorado School of Medicine announces a $2500 essay prize—The Cochems Competition in Thrombophlebitis and Basic Vascular Problems The prize will be awarded to the author of the best paper in the above mentioned field Basic vascular problems under consideration in this instance should be concerned with the underlying mechanisms or processes of vascular disease particularly those associated with thrombosis but not necessarily restricted to it

The competition is open to all persons holding the doctorate degree who are subject to U.S tax regulations. Entries must be received no later than November 30 1975 Address inquiries to Dean School of Medicine University of Colorado Medical Center 4200 East Ninth Ave Denver Colo 802?0

Thirteenth annual cardiology seminar

The Rogers Heart Foundation will sponsor the Thirteenth Annual Cardiology Seminar at the Macuto Sheraton Hotel Caracas, Venezuela from December 2 through 5 1975 Faculty will include John A Kastor M D Philadelphia Frank LaCamera Jr M D St Petersburg David Lauler M D New York Henry J L. Marriott M D St Petersburg Roger F Palmer M D Miami Brendan Phibbs, M D Tucson Mauricio Rosenbaum M D Buenos Aires Mark E Silverman M D Atlanta Jane Somerville M D F R C P., London Walter Somerville M D F R C P London and Edward Swanick M D St Petersburg For further information on the seminar please write The Rogers Heart Foundation 601 12th Street North, St Petersburg Fla 33705 Telephone (813) 894 0790

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Annual Review of Medicine Selected Topics in the Clinical Sciences Edited by William P Creger C H Coggins, and E. W Hancock Palo Alto Calif 1975 598 Annual Reviews, Inc 598 pp

Normal Conduction System and the Electrocardiogram Programmed Instruction Unit By Nancy Fairchild Clark, R N Philadelphia 1975 F A Davis Company 96 pp Price $3 95

Announcements

Pediatric and adolescent echocardiography course

The Department of Pediatrics University of Arizona will present a didactic and practical course in one and two dimensional pediatric echocardiography November 14 to 16 1975 The meeting is timed to just precede the American Heart Association meetings in Anaheim Two types of registration are available (1) Didactic only (2) Didactic plus 9 hours experience with one and two dimensional instrument systems Course faculty include S J Goldberg M D H D Allen M D D J Sahn M D W L Henry M D J M Griffith M S E E and R Solinger M D

For further information contact S J Goldberg Department of Pediatrics, University of Arizona School of Medicine Tucson Ariz 85724

Jane Nugent Cochems competition

The University of Colorado School of Medicine announces a $2500 essay prize—The Cochems Competition in Thrombophlebitis and Basic Vascular Problems The prize will be awarded to the author of the best paper in the above mentioned field. Basic vascular problems under consideration in this instance should be concerned with the underlying mechanisms or processes of vascular disease particularly those associated with thrombosis but not necessarily restricted to it

The competition is open to all persons holding the doctorate degree who are subject to U.S tax regulations. Entries must be received no later than November 30 1975 Address inquiries to Dean School of Medicine University of Colorado Medical Center 4200 East Ninth Ave Denver Colo 80220

Thirteenth annual cardiology seminar

The Rogers Heart Foundation will sponsor the Thirteenth Annual Cardiology Seminar at the Macuto Sheraton Hotel Caracas, Venezuela from December 2 through 5 1975 Faculty will include John A Kastor M D Philadelphia Frank LaCamera Jr M D St Petersburg David Lauler M D New York Henry J L Marriott M D., St Petersburg Roger F Palmer M D Miami Brendan Phibbs, M D Tucson Mauricio Rosenbaum M D Buenos Aires Mark E Silverman M D, Atlanta Jane Somerville M D F R C P London Walter Somerville M D F R C P London and Edward Swanick, M D St Petersburg For further information on the seminar please write The Rogers Heart Foundation 601 12th Street North St Petersburg Fla 33705 Telephone (813) 894 0790

Editorial

Surgical management of severe mitral valve disease in childhood

M S Gotsman MD FRCP
R. L. Van der Horst M Med (Paed)
Durban Natal, South Africa and Jerusalem Israel

Acute rheumatic fever is common in Asia Africa and the underprivileged groups in the western countries The disease has a malignant course and the natural history is accelerated so that severe established mitral valve disease with important clinical consequences occurs in childhood, recurrent episodes of cardiac failure require repeated and prolonged hospitalization and death often occurs before the age of 20 years [1]

The acute rheumatic process appears to be related to poor socioeconomic conditions over crowding failure of early treatment of streptococcal infections, maldistribution of medical care and lack of understanding by patients that long term chemoprophylaxis is essential to prevent recurrent attacks It is possible that these patients have a different immunological response and that the disease slumbers and never disappears after the initial episode

Mitral stenosis with severe valve obstruction is often established before the age of 15 usually without an antecedent episode of acute rheumatic fever [2,3] The valve may calcify early and significant calcification is present in 10 per cent of these patients by the age of 15 Severe pulmonary arterial hypertension is a function of critical mitral valve obstruction and is related to the left atrial pressure Atrial fibrillation is uncommon but when present it is associated with severe obstruction and leads to abrupt deterioration in clinical state often with acute pulmonary edema A few patients have such severe pulmonary hypertension that they present as a diagnostic problem right ventricular hypertrophy and failure with tricuspid incompetence dominate the clinical picture In these patients clinical exclusion of mitral incompetence may be impossible and they require cardiac catheterization and angiocardiography before surgery

Management is by closed instrumental mitral valvulotomy using a transventricular dilator and is indicated in all patients with significant obstruction The pulmonary hypertension recedes within a week of an adequate operation but takes a further three months to return to the range of normal Restenosis may occur within 5 to 7 years Patients with light calcification of the valve an important jet of mitral incompetence or restenosis are not suitable for closed valvulotomy since they have thick fibrotic valve cusps with extensive disease of the chordae and subvalvular mechanism

We have studied groups of children before and after the operation by cardiac catheterization and left ventricular angiocardiography and in the absence of acute carditis we have not been able to demonstrate any abnormality of left ventricular function

Young patients who present with severe established mitral incompetence or mixed mitral valve disease usually give a history of several episodes of acute rheumatic fever with active carditis The pathology is fairly constant pure mitral incompetence is a consequence of shortening and rolling of the posterior cusp and its chordae tendineae so that the anterior cusp wafts past an unimpressive posterior buttress while mixed mitral valve disease is associated with a fishmouth orifice due to chordal and commissural fusion with extensive shortening of the cusps and of the subvalvular tissue Mild mitral incompetence is well tolerated

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Editorial

Surgical management of severe mitral valve disease in childhood

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Acute rheumatic fever is common in Asia, Africa, and the underprivileged groups in the western countries. The disease has a malignant course and the natural history is accelerated so that severe established mitral valve disease with important clinical consequences occurs in childhood; recurrent episodes of cardiac failure require repeated and prolonged hospitalization and death often occurs before the age of 20 years.[1]

The acute rheumatic process appears to be related to poor socioeconomic conditions, overcrowding, failure of early treatment of streptococcal infections, maldistribution of medical care, and lack of understanding by patients that long-term chemoprophylaxis is essential to prevent recurrent attacks. It is possible that these patients have a different immunological response and that the disease slumbers and never disappears after the initial episode.

Mitral stenosis with severe valve obstruction is often established before the age of 15, usually without an antecedent episode of acute rheumatic fever.[2,3] The valve may calcify early and significant calcification is present in 10 per cent of these patients by the age of 15. Severe pulmonary arterial hypertension is a function of critical mitral valve obstruction and is related to the left atrial pressure. Atrial fibrillation is uncommon but when present it is associated with severe obstruction and leads to abrupt deterioration in clinical state, often with acute pulmonary edema. A few patients have such severe pulmonary hypertension that they present as a diagnostic problem; right ventricular hypertrophy and failure with tricuspid incompetence dominate the clinical picture. In these patients clinical exclusion of mitral incompetence may be impossible and they require cardiac catheterization and angiocardiography before surgery.

Management is by closed instrumental mitral valvulotomy using a transventricular dilator and is indicated in all patients with significant obstruction. The pulmonary hypertension recedes within a week of an adequate operation but takes a further three months to return to the range of normal. Restenosis may occur within 5 to 7 years. Patients with light calcification of the valve, an important jet of mitral incompetence, or restenosis are not suitable for closed valvulotomy, since they have thick fibrotic valve cusps with extensive disease of the chordae and subvalvular mechanism.

We have studied groups of children before and after the operation by cardiac catheterization and left ventricular angiocardiography and in the absence of acute carditis we have not been able to demonstrate any abnormality of left ventricular function.

Young patients who present with severe established mitral incompetence or mixed mitral valve disease usually give a history of several episodes of acute rheumatic fever with active carditis. The pathology is fairly constant: pure mitral incompetence is a consequence of shortening and rolling of the posterior cusp and its chordae tendineae so that the anterior cusp wafts past an unimpressive posterior buttress, while mixed mitral valve disease is associated with a fishmouth orifice due to chordal and commissural fusion with extensive shortening of the cusps and of the subvalvular tissue. Mild mitral incompetence is well tolerated

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for many years but severe incompetence imposes a large volume load on the left ventricle unless there is associated acute carditis left ventricular function is normal (ejection fraction, LVEDP, LV dp/dt)[6,7] The over all left ventricular stroke volume is increased but most is regurgitated into the left atrium The forward (or effective) stroke volume is low and the left atrial "V" wave is tall (40 to 70 mm Hg) This is associated with pulmonary venous hypertension and shortness of breath the pulmonary artery pressure is related to the mean LA pressure and severe pulmonary hypertension is not uncommon Intercurrent chest infections further episodes of acute rheumatic carditis and the onset of atrial fibrillation precipitate severe cardiac failure

The clinical pattern is no different from that observed in adults and the degree of incompetence can be assessed from the size of the heart (on palpation and on x ray) a palpable left atrial lift the presence of a pathological third heart sound and an apical mid diastolic decrescendo flow murmur with also a wide splitting of S (due to abbreviation of left ventricular systole which is proportional to the forward stroke volume) and accentuation of pulmonary valve closure[7,8] The chest x ray is of great value and heart size and volume, left atrial and ventricular enlargement and signs of pulmonary venous and arterial hypertension are related to the severity of the mitral incompetence

Mitral valve replacement is indicated in patients who have severe disability (Grade III or IV) or who have lesser disability but other signs of very severe valve incompetence as assessed by physical examination, ECG or chest x ray Forty per cent have important additional tricuspid valve disease and 10 per cent have involvement of the aortic valve Patients should be in an optimum clinical state at the time of operation digitalis diuretics and prolonged bed rest will ameliorate cardiac failure and steroids will allow active carditis to subside The improvement in clinical state after rest in bed is quite dramatic, but deceptive since disability and severe cardiac failure often return when the children are permitted to resume normal activity or cease to take medication

Operative mortality is low (10 per cent) provided that patients are prepared carefully and complications after operation are uncommon[1,8,12]

The ideal valve prosthesis has not been found In a series of 100 patients we have had experience of replacing the mitral valve with a Hammersmith Starr Edwards Beall, Lillehei Kaster, and mounted inverted aortic homograft prostheses In mitral incompetence the valve annulus is dilated and it is possible to insert a valve with a large orifice area (Starr Edwards No 3 or 4) but in the presence of stenosis the orifice is small (Starr Edwards No 2) The smaller prosthetic valves have an important gradient at normal flow rates, and this may increase further on exercise the left atrial pressure is elevated and residual postoperative radiological cardiac enlargement is common The hemodynamic response is as good with the Beall valve, and probably slightly better after insertion of a tilting disc Lillehei Kaster prosthesis[12] The Beall valve causes early hemolysis in the immediate postoperative period but this decreases after a few days The best hemodynamic response is achieved by replacement of the valve with a fresh inverted aortic valve homograft mounted on a stent The residual gradient across an 18 mm (small) prosthesis is 2 or 3 mm Hg The clinical response is dramatic and heart size returns to normal within one month of operation The only problem is the durability of the valve the life of a chemically sterilized and mounted valve is 3 to 5 years in most patients A fresh antibiotic sterilized valve appears to be more durable[14]

Patients can expect to return home three weeks after operation and be back at school a month later

Atrial fibrillation should be restored to sinus rhythm one month after operation by quinidine or electroconversion and the patient maintained on quinidine chemoprophylaxis for three months The average response to valve replacement is so dramatic that residual symptoms or radiological cardiac enlargement three months after operation must be attributed to cardiac or valvular dysfunction a small valve (small primary secondary or tertiary orifices) thrombosis or tissue ingrowth on the valve seat ball disc or homograft malfunction valvular insufficiency (prosthetic or cusp inadequacy), involvement or progression of lesions on other valves or further attacks of acute rheumatic fever Postoperative cardiomyopathy (ventricular dysfunction) occurs and is responsible for residual symptoms or unexplained cardiac enlargement[13,14] It may be due to

multiple emboli myocardial hypoxemia during perfusion or to prolonged postoperative rheumatic carditis Postoperative prosthetic bacterial endocarditis is a constant danger Systemic emboli from the metallic valves occur and can be avoided by anticoagulant therapy It is interesting that we did not use anticoagulants routinely and emboli were uncommon [17]

The patients need careful postoperative supervision Penicillin chemoprophylaxis must be continued and the patient monitored for residual symptoms cardiac enlargement alterations in cardiac signs and minor embolic episodes Minor disease in other valves may progress and become significant in the course of 1 to 2 years When mitral incompetence occurs after homograft valve replacement it appears abruptly often with a palpable thrill but progress is slow (weeks) and the valve can be replaced electively

The over all results are impressive and although the ideal valve has not been designed valve replacement should be undertaken in patients with important valve disease to spare the child from severe cardiac disability possible death and to permit him to lead a more normal life

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Clinical communications

Incidence of arrhythmias and ST-segment changes in elderly patients during barium enema studies

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There is little information relative to the incidence of potentially serious cardiac arrhythmias and ST segment alterations that may occur during barium enema x ray studies Further, the factors predisposing to such arrhythmias and repolarization abnormalities have not been adequately identified The purpose of our study was to document the incidence of arrhythmias and significant ST segment depression in an unselected older population of patients (over age 60) utilizing the continuous electrocardiographic (ECG) monitoring technique In addition we sought to examine the effects of glucagon on such ECG abnormalities since this drug is often given to reduce gastrointestinal spasm and to identify the ECG and physiologic factors that are predictors of ECG abnormalities during the barium enema

Methods

Fifty eight consecutive patients over the age of 60 (range, 60 to 98) who were having a routine barium enema examination were studied Patients were prepared with laxatives the night before followed by cleansing enemas on the morning of the x ray Immediately before the barium enema a routine 12 lead ECG was performed In addition a resting 100 cycle rhythm strip was obtained and the cardiac rhythm was recorded during the Valsalva maneuver and its recovery phase The systemic arterial pressure also was measured in the supine and upright positions with a cuff sphygmomanometer During the barium study, continuous ECG tape recordings were obtained with a Holter Avionics Electrocardiorecorder, Model 350 F An Avionics Millivolt Calibrator, Model 356A, permitted subsequent analysis of ST segment changes

The patient was selected at random to (1) receive glucagon (1 mg intravenously preceding the barium study) or (2) enter in a control group by a radiologist who had not seen the ECG data The barium enema examination was performed in the usual fashion During each phase of the test the presence or absence of symptoms was recorded After the barium study, a repeat 12 lead ECG was obtained The cardiologist who interpreted the continuous ECG monitor tracings was not aware of the patient s clinical diagnosis or whether or not glucagon had been given

'Positive' alterations in the continuous ECG were defined as (1) New atrial tachyarrhythmias which did not include ectopic atrial rhythm or wandering atrial pacemaker Thus, atrial arrhythmias considered to be significant were supraventricular tachycardia and atrial fibrillation (2) Any form of sinus arrest with an escape rhythm (3) Premature ventricular contractions (PVC s) occurring at a frequency of more than 7 per minute and 7 per 100 cycles multifocal PVC s within 8 seconds of each other, PVC s in pairs or ventricular tachycardia Episodes of bigeminy, trigeminy, and quadrigeminy that did not satisfy the criteria of 7 PVC s per minute were not considered to be a positive finding (4) ST segment depression of greater than 1 0 mV

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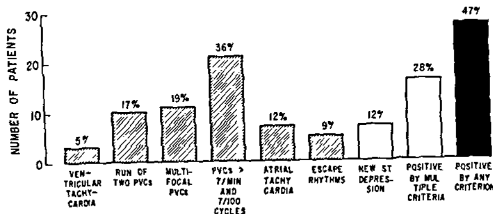


Fig 1 The incidence of new arrhythmias and ST segment depression in 58 patients Each of the arrhythmias described in the figure constituted a positive ECG response (see text)

persisting for 80 msec during the continuous ECG monitor recording However if a repolarization abnormality was present on the patient s resting ECG or if the patient was receiving digitalis then 2 0 mV of additional ST segment depression was required[1 2]

In addition a total ectopic activity index defined as the ratio of nonsinus beats per 100 cycles in the pre-barium enema rhythm strip was calculated A second ectopic activity index was derived from the 100 consecutive cycles containing the most frequent ectopic activity recorded during the continuous ECG monitor obtained at the time of the barium enema A third ectopic activity index relating only to the number of PVC s per 100 consecutive cycles was computed for both the rhythm strip and the continuous ECG monitor

Results

ECG findings Of the 58 patients studied 27 had significant alterations in their ECG recordings as defined above The incidence of new arrhythmias and ST segment changes in the 58 patients is depicted in Fig 1 Twenty three patients had positive studies on the basis of the development of significant arrhythmias during the barium enema (Figs 2 to 4) Four additional patients were considered to be positive because of new ST-segment changes (Fig 5) In 16 of the 58 patients (28 per cent) the ECG was considered to be positive based on multiple criteria (Fig 6) Thirty-one patients had negative studies including three patients with atrial arrhythmias that were present before the study and one patient who had both pre existing atrial fibrillation and a permanent transvenous pacemaker

Factors predictive of new arrhythmias

Age Table I shows the appearance of significant alterations in the ECG recording as a function of age distribution by decade In general more positive tests occurred in the older patients ($p < 0.05$ χ^2 analysis) however the marked variation in each age group suggested the need for more specific predictive factors

Resting ECG The finding of any ectopic activity on the baseline ECG exhibited a statistically significant association with new ventricular arrhythmias ($p < 0.001$ χ analysis Table II) however ectopic activity on the resting ECG was not a predictor of new ST segment depression Only 7 of 44 patients (16 per cent) had ectopic beats on the 12 lead ECG obtained after the barium enema when none was present on the initial record Conversely all of the patients with ectopic beats on the initial ECG also demonstrated ectopic activity on the ECG obtained after the barium enema

Seventeen of 18 patients with a ventricular ectopic index of 1 or more determined on 100 cycle rhythm strip recorded prior to the barium enema subsequently exhibited ventricular arrhythmias as contrasted with only four patients who developed ventricular ectopia among 40 patients with a baseline ventricular ectopic index of zero ($p<0.001$ Table II Fig 7) Of 31 patients with a *total* ectopic activity index of zero prior to the barium enema only three had a significant ventricular arrhythmia during the barium enema Thus as a predictor of a *negative* ECG during the

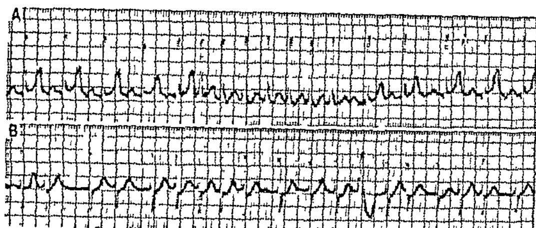


Fig 2 ECG recordings from two different patients who developed atrial arrhythmias during the barium enema are illustrated *Panel A* Paroxysmal atrial tachycardia *Panel B* Paroxysmal atrial fibrillation

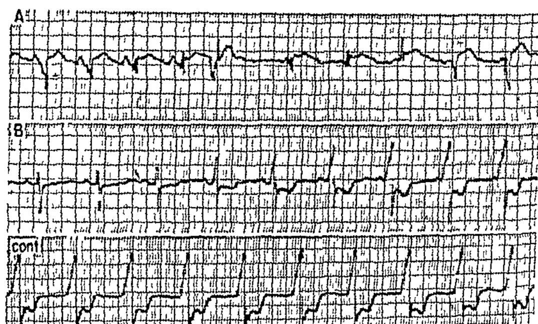


Fig 3 *Panel A* Sinus rhythm is interrupted by a PVC which is followed by a junctional escape rhythm for three beats that is terminated by an ectopic atrial rhythm *Panel B* Atrioventricular dissociation with a wide QRS complex that may represent either a junctional focus or an accelerated ventricular rhythm

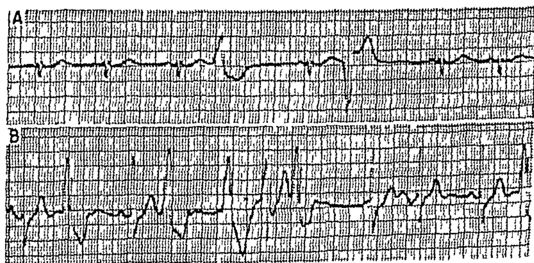


Fig 4 *Panel A* Multifocal PVC s occurring within 2 seconds *Panel B* Ventricular tachycardia occurring during the barium enema The patient was asymptomatic

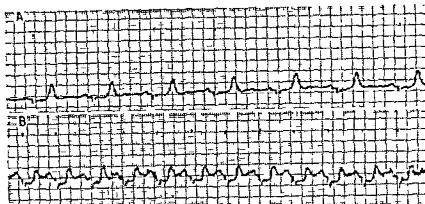


Fig 5 Panel A Normal ST segments are present during the 100 cycle rhythm strip obtained prior to the barium enema. *Panel B* Significant ST segment depression associated with a heart rate of 94 beats per minute during the barium enema The patient had no chest pain during the study

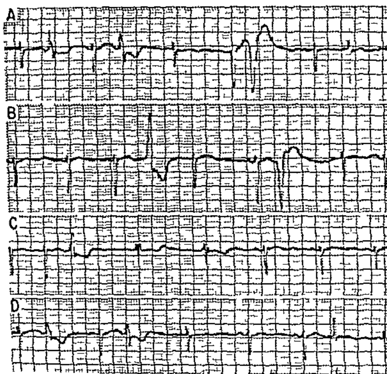


Fig 6 Panels A through D are from the same patient who met multiple criteria for a positive ECG response including supraventricular and ventricular premature contractions multifocal PVC s two PVC s in a row and sinus arrest followed by junctional escape beats

barium enema this observation is highly significant ($p<0.001$ Table II)

Fig 7 depicts the relation of a ventricular ectopic activity index of 1 or more on the rhythm strip before the barium enema to the occurrence of significant ventricular arrhythmias during the barium enema These data indicate that the presence of even one PVC on a resting 100 cycle rhythm strip has a highly significant predictive value Conversely the lack of any PVC s on such a rhythm strip correlates with the absence of significant ventricular ectopic activity during the barium enema

Of the 40 patients with a pre-barium enema ventricular ectopic activity index of zero 21 developed PVC s but did not meet our criteria for significant ventricular ectopic activity The other 15 patients exhibited no ventricular ectopic

Table I Age distribution of patients

ECG findings	Age			
	60 69	70 79	80 89	90 99
Negative ECG during barium enema	19	6	5	1
Positive ECG during barium enema	6	8	13	0
V only	2	1	1	–
A only	0	1	1	–
ST only	2	2	0	–
V + any other criterion	2	4	11	–

V = ventricular arrhythmia A = atrial arrhythmia ST = new ST segment depression For definition of positive" and negative ECG findings, see text

Table II Arrhythmias during barium enema

ECG findings*	True positive	False negative	Significance (χ^2 test)
Baseline ECG with any ectopic activity			
V only	12/14	9/44	$p < 0.001$
V + A	13/14	10/44	$p < 0.001$
V + A + ST	13/14	14/44	$p < 0.001$
Ectopic activity index of 1 or more PVC/100 cycles			
V only	17/18	4/40	$p < 0.001$
Ectopic activity index of zero on the 100 cycle rhythm strip			
V only	3/31	18/27	$p < 0.001$
V + A	3/31	20/27	$p < 0.001$
V + A + ST	4/31	23/27	$p < 0.001$

PVC = premature ventricular contraction V = ventricular arrhythmia A = atrial arrhythmia ST = new ST segment depression p = probability True positive = ratio of patients with positive ECG findings (see text) on the continuous ECG tape during the barium enema to patients exhibiting ectopic activity on the baseline ECG or rhythm strip False negative = ratio of patients with positive ECG findings on the continuous ECG tape monitor to patients exhibiting no significant ectopic activity on the baseline ECG or rhythm strip

activity during the x ray study Conversely, among the 21 patients who developed significant ventricular arrhythmias during the barium study, only three satisfied the criteria for significant ventricular ectopic activity on the resting rhythm strip as well In each case these patients developed multiple positive criteria (atrial arrhythmias complex ventricular arrhythmias, ventricular escape beats) during the barium enema

Prior heart disease Twenty seven of 58 patients had a history of pre existing organic cardiac disease All 27 patients either were receiving cardiac medications (digitalis diuretics antiarrhythmic or beta blocking agents), or had findings of left ventricular enlargement by either ECG or x ray Whether such clinically evident

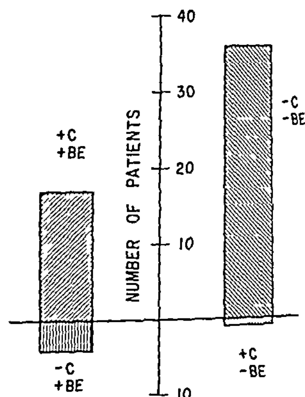


Fig 7 A comparison of the presence (+) or absence (–) of PVCs on the control 100 cycle rhythm strip *(C)* with the presence (+) or absence (–) of ventricular arrhythmias during the barium enema *(BE)*

heart disease was present or absent had no predictive value Thus 15 of 27 patients with a history of heart disease developed significant ECG abnormalities during the barium enema compared with 12 of 31 patients without a history of cardiac disease ($p > 0.30$) Seventeen of 58 patients were receiving a digitalis preparation at the time of this study Nine of these 17 patients exhibited positive ECG findings during the barium enema contrasted to 18 of 41 patients who were not receiving digitalis ($p > 0.70$)

Effect of glucagon Thirty randomly chosen patients received 1 mg of glucagon intravenously to reduce intestinal spasm Ten of the 30 patients receiving glucagon developed ventricular arrhythmias as compared to 11 of 28 patients who did not receive the drug ($p > 0.70$) The incidence of atrial arrhythmias and ST segment changes also did not differ between the two groups

Postural hypotension Fourteen of 54 patients had a decrease of greater than 30 mm Hg of systolic arterial pressure upon assuming the erect position or a systolic blood pressure of less than 90 mm Hg while standing Eleven of 14 patients with this finding compared with 15 of 40 patients without this finding developed significant ECG changes during the barium enema when all criteria were considered ($p < 0.01$)

Additional correlations Five patients who exhibited escape rhythms during the barium enema all had significant ventricular arrhythmias during the barium enema as well These five patients were all receiving digitalis In these five individuals the Valsalva maneuver performed prior to the barium enema failed to produce an escape rhythm However in two of the 58 patients studied sinus pauses with ventricular or junctional escape beats occurred following the Valsalva maneuver Both of these patients had no significant arrhythmias or ST segment depression during the barium enema

Multifocal PVC s occurring within 8 seconds of each other were observed only in patients who met the general criteria for significant ventricular arrhythmias as well Five of these patients were not receiving cardiac medications and did not have a prior history of cardiac disease

Discussion

Previous studies have suggested that ECG abnormalities are more frequently encountered during a barium enema x ray study in patients over the age of 60 and in patients with documented heart disease Utilizing radioelectrocardiography Eastwood[3] reported that 16 of 95 patients in all age groups exhibited potentially dangerous arrhythmias such as frequent or coupled premature ventricular contractions transient sinus arrest atrioventricular block new ST segment depression or bundle branch block However in his series 13 of 56 patients over age 60 accounted for 81 per cent of these arrhythmias The remaining 44 patients showed only minor abnormalities such as premature atrial contractions and rare unifocal PVC s Berman and associates[4] studied 62 randomly chosen patients 33 of whom were over the age of 60 Ten patients exhibited significant ECG changes including six with ST segment depression and four with arrhythmias All 10 of these patients were over age 60 and all had a prior history of cardiac disease Using direct ECG monitoring Stemple and Montgomery studied 38 patients (average age 69 years) of whom eight developed premature contractions during all phases of the barium enema however they reported no sustained arrhythmias Nevertheless they observed ST segment alterations in half of the patients but did not comment on the magnitude of these changes.

Because earlier work indicated that a higher incidence of arrhythmias would be found in older patients we confined our study to consecutive patients over the age of 60 The continuous ECG monitoring technique has the advantage over previously employed methods because the arrhythmias are recorded and stored permitting later analysis of the record Use of this methodology may explain the higher incidence of dangerous arrhythmias observed in our study compared with previous reports in which direct on line visualization of the ECG was utilized With the latter technique it is possible that the maneuvers employed during the barium enema were influenced by the arrhythmias observed whereas in our study the radiologist was unaware of the occurrence of serious arrhythmias Nevertheless all patients tolerated the x ray examination well and no cardiac symptoms were noted during the barium study Thus it is likely that despite the high incidence of potentially dangerous arrhythmias catastrophes such as ventricular fibrillation sudden death or myocardial infarction are very unusual events

Our criteria for the definition of serious ventricular arrhythmias were derived from studies in which continuous ECG monitoring was employed in the study of patients after acute myocardial infarction[6,7] In 160 such patients Kotler and associates[6] reported a *sixfold increase in the* mortality rate due to sudden death among patients who demonstrated significant ventricular arrhythmias on the continuous tape recording Because we did not study a homogeneous group of patients i e subjects with proved coronary artery disease we employed criteria requiring 7 PVC s per 100 cycles or more rather than 1 PVC per 500 cycles in order to score a test positive by the PVC response alone Otherwise our other criteria are similar to those previously described by Crawford and associates[7] who reported that a combination of 12 hour continuous ECG monitoring the resting ECG and a treadmill exercise test yielded a 46 per cent incidence of positive ECG findings in postinfarction patients In our patients continuous ECG monitoring during a barium enema (usually a 10 to 45 minute time period) revealed that 47 per cent had positive ECG findings despite the fact that only 8 of our 58 patients (14 per cent) had a previous documented acute myocardial infarction Whether the patients in our study who had positive ECG findings are at increased risk for sudden death as noted in previous studies[6,8,10] requires further investigation

The mechanism of arrhythmia production and ST segment depression may be explained in a variety of ways The preparation of the patient for the barium enema involves a procedure which often produces dehydration Thus, many patients showed definite postural blood pressure changes Our data suggest that such alterations in systemic arterial pressure are an important factor predictive of subsequent arrhythmias and ST-segment depression These blood pressure changes seem to occur independently of ventricular premature beats or other ectopic activity present on the resting tracing Further, dehydration, fear, and pain during the procedure likely stimulate catecholamine release which increases the heart rate and frequency of ectopic beats New ST segment depression (which often correlated with postural blood pressure alterations) usually occurred at heart rates greater than 140 beats/minute, again suggesting catecholamine stimulation The effect of evacuation of the barium and of distention of the colon had little influence on our results In this connection, a controlled Valsalva maneuver produced significant ECG changes in only two patients, both of whom had no ECG abnormalities during the barium enema

In the age group studied, a prior history of cardiac disease was *not* associated with a positive ECG during the barium enema Nearly half of the patients without a history of heart disease still had positive ECG findings by our criteria Certainly, it is possible that the barium enema may provide a stress to the patients in this age group with latent cardiac disease that approaches the treadmill test in the production of arrhythmias Conversely, patients with cardiac disease under more controlled medical management, may have been in a better state of cardiovascular compensation prior to the barium enema A 1 mg intravenous dose of glucagon had no effect on the incidence of arrhythmias or ST segment changes, suggesting that gastrointestinal spasm plays little or no role in the production of ECG abnormalities

In summary, this study indicates that the physician who requests a barium enema examination should take certain precautions to identify patients at high risk for potentially serious cardiac arrhythmias The patient over age 60, with a prior cardiac history, pre existing ectopic beats on a resting ECG, and significant postural changes in systolic systemic arterial pressure, should be considered at risk for such arrhythmias during a barium enema As an additional measure, a 100 cycle rhythm strip obtained on the morning of the barium enema increases predictive reliability, since the patient with no ectopic beats on the 100 cycle rhythm strip and no postural blood pressure changes is unlikely to develop ECG changes during the barium enema despite other abnormalities on ECG or a history of cardiac disease Once the patient at risk has been identified the physician should consider the possibilities of further cardiac evaluation, antiarrhythmic drug therapy, and ECG monitoring during the barium enema In addition, the radiologist should be alerted to the possible occurrence of arrhythmias and repolarization abnormalities during the procedure

We wish to thank Ms Lynn Gorum and Mr Dan Haas for their technical assistance

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Twenty four hour automatic monitoring of blood pressure and heart rate at work and at home

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The routine measurement of blood pressure in a physician s office on a given day represents a very small sample of the 1 440 indirect measurements which could be obtained if measurements were made in that subject every minute over 24 hours including sleep Although the indirect method of measurement has been in use for nearly 70 years automatic monitoring by this method of subjects in their usual environment has not been accom plished In 1964 Kain Hinman and Sokolow described a portable device which however required mechanical involvement on the part of the subject and therefore would not allow for recordings in situations such as car driving eating or while sleeping at home In 1968 Bevan Honour and Stott reported 24 hour ambulatory direct blood pressure measurements in 22 sub jects all but four being hospitalized patients Since 1968 we have developed a fully automatic portable device light in weight and of proved accuracy (1974) For the first time it has been practical to measure indirect pressures in a fully automatic fashion in subjects at work at home and during sleep at home This report consists of 24 hour recordings at 15 minute intervals for five subjects in which the data are related by a tape recorded diary to physical activity car driving eating and sleeping

Methods and subjects

The device A fully automatic portable device weighing 4 pounds and about the size of an average medical text records systolic and dia stolic pressures and heart rates in subjects wherever they might be An electronic timer which is programmable for intervals ranging from 6 to 20 minutes initiates the start signal causing the tape deck to begin its 1 minute cycle Mechan ically linked to the tape drive mechanism is a force pressure translator which provides a linear pressure change from 240 to 40 mm in a conven tional cuff The pressure points are modulated onto magnetic tape in 10 mm Hg steps The incidence of Korotkoff sounds obtained from a crystal contact microphone further modulates the pressure information giving a record that yields pressures and heart rates on playback An audio track records the subject s verbal report of activity and events at the time of each pressure recording A pressurized N_2 source and a re chargeable battery allow for 50 measurements Tape length allows for about 40 recordings and is the limiting factor Several safety devices are incorporated to prevent abnormal or sustained pressures at the cuff Recorded pressures were within 5 per cent of simultaneously recorded auscultatory values measured in a variety of subjects The device is unique in that the subject is mechanically uninvolved and a pressure scale is recorded with each pressure measurement The lengths of the inflation tubing and the two micro phone wires are such as to allow the recorder to be placed on a desk on a chair side table on a bed side table on the car seat or to be carried by means of a shoulder strap like a camera as the subject moves about

The procedure The crystal microphone was taped in place over the left brachial artery to pick up the Korotkoff sounds and was covered with a conventional sphygmomanometer cuff taped to the arm to prevent slipping The inflation tube was connected to the recorder and the crystal

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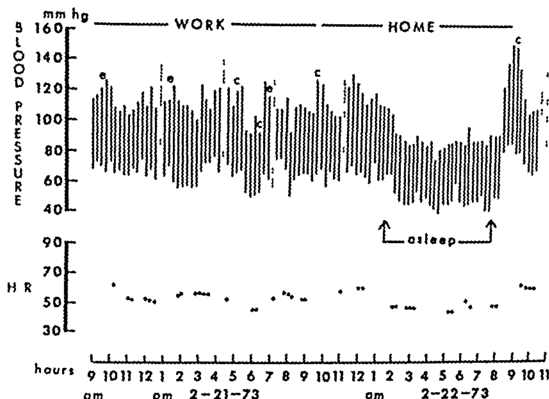


Fig 1 A 26 hour record of blood pressures (solid bars for inactivity interrupted bars for activity circumstances) and heart rates (solid dots for inactivity and open circles for activity circumstances) at 15 minute intervals for a 55-year-old physician at work and at home F signifies eating periods and C values obtained while driving a car Figs 2 to 5 are similarly depicted

microphone and the voice microphone lines were plugged in The timer was set to provide a recording every 15 minutes The subject was instructed to stop any activity and keep the left arm still during the 50 to 60 seconds required for inflation and deflation of the cuff While recording the blood pressure the voice microphone is open, the subject was asked to state the time whether he was physically active or inactive at that time, and what he was doing for the preceding 2 minutes and whether he had any symptoms The starting time for the 24 hour period varied with the subject s convenience Three subjects started at 8 A M, one at 12 noon and one at 2 P M Without changing the cuff, each returned about 8 hours later and the original recorder was disconnected and a second recorder substituted A third recorder was given to the subject to be substituted for the second recorder, usually being connected at 10 to 11 P M at home Changing recorders simply involved disconnecting the tube and two jacks and reinserting them into the unused recorder Flipping a toggle switch under the cover caused the recorder to begin its automatic recordings After the subject retired, he was assumed to be asleep when no voice was recorded

The subjects Subject 1 was a physician, age 55 in apparent good health His day was spent in clinical and administrative office duties

Subject 2 was a biostatistician, age 49 in good health He spent his day in office work with considerable walking between buildings on two campuses

Subject 3 was a 49 year old electronics technician working with Subject 5 in a hospital laboratory He had had a myocardial infarction 8 years ago Because of unstable angina, he was taking 25 mg of propranolol four times daily and was doing so at the time of the 24 hour recording His day was spent in the laboratory, often seated but with occasional mild physical activity

Subject 4 was a 40 year old pharmacologist He has essential hypertension and for 9 months including the day of the recording has been taking 50 mg of hydrodiuril twice daily His day was spent in his laboratory and office with minimal physical activity

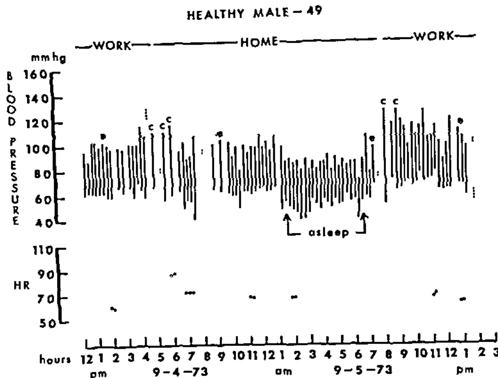


Fig 2 A 26 hour recording of blood pressures and heart rates at 15 minute intervals for a 49 year-old healthy biostatistician

Subject 5 was a 63 year old electronics technician who has emphysema but was taking no medications His day involved mild physical activity in and about the laboratory as well as sedentary bench work there

Results

Subject 1 Fig 1 shows all pressures and heart rates recorded for a 26 hour period for the 55 year old physician while working in a medical center and while at home He was on no medications except for 5 mg of diazepam prior to sleep Physical activity involved walking otherwise his day was spent working in his office performing clinical duties, and attending meetings It is evident that he is normotensive over the 26 hours excluding sleep his blood pressure averaged 120/67 mm Hg with a mean heart rate of 65 beats per minute The 6 5 hour sleep period was accompanied by a considerable fall in pressure with a mean of 88/49 and a mean heart rate of 48 without much variation in either Only a very slight increase in systolic pressure is noted during eating and in contrast car driving was associated mainly with a relative tachycardia With two exceptions, activity (walking) had only modest effects on pressure with slight tachycardia in most instances The highest resting pressures were recorded in the first couple of hours after awakening

Subject 2 Fig 2 a 26 hour record for the 49 year old statistician is characterized over all by low normal pressures and rather variable resting heart rates while awake He was often physically active chiefly walking but of the 20 activity values only two showed significant elevation in the systolic values and modest tachycardia His over all blood pressures while awake were rather low averaging 107/64 with a mean heart rate of 78 During 5 hours of rather restless sleep his pressures fell less than those of Subject 1 averaging 86/53 with an average heart rate of 67 with little variability in either Pressures and rates did not vary while eating Car driving was associated with slight increases in systolic pressures and heart rates

Subject 3 Fig 3 shows all values for 24 hours for the 49 year old technician who was taking propranolol 25 mg four times daily Earlier 8 hour daytime recordings prior to propranolol treatment had shown considerable variation in pressures at times at hypertensive levels with

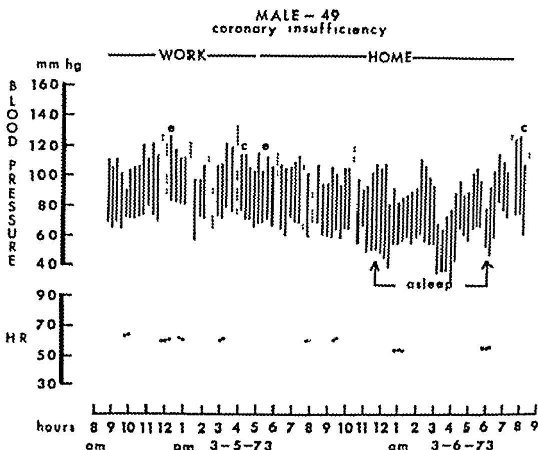


Fig 3 A 24 hour recording of blood pressures and heart rates at 15 minute intervals for a 49 year old laboratory technician who had coronary artery disease The subject was taking propranolol 25 mg four times daily

resting heart rates in the range of 80 to 90 per minute This record is in sharp contrast and shows a reduced variability in pressures and heart rates especially the latter, related most likely to his medication Physical activity, involving walking showed modest increases in systolic values for the most part Activity was not associated with an increase in heart rate His mean blood pressure throughout, excluding sleep, was 113/72 with a mean heart rate of 62 His sleep period described as restful was remarkable for the considerable variation in pressures but with very little change in heart rate with values averaging 91/55 and 55 per minute Eating was not accompanied by changes in pressure or heart rate The same was true on the three occasions when he drove his car

Subject 4 Fig 4 shows the data for a 26 hour period in the 40 year old pharmacologist with mild essential hypertension who was receiving a diuretic agent As might be expected his pressures, especially diastolic were somewhat higher in general than those seen in the other four subjects The record shows rather good control of his pressures in general with three exceptions where hypertensive levels were reached on two occasions at work in both instances while physically inactive but dealing interpersonally with professional associates and one such elevation at home While awake his over all pressures averaged 128/80 with an average heart rate of 77, the latter showing only modest variability between successive measurements During 7 5 hours of sleep at home both pressures and rates fell considerably with average values of 91/60 and 55 per minute In absolute terms this represented the greatest fall in values in the group during sleep There were only three records during activity, chiefly walking and in only one of these was there a significant change in pressure with widening of the pulse pressure and tachycardia Eating was unassociated with significant changes in either pressure or rate A modest increase in heart rate only is noted while driving

Subject 5 Fig 5 shows the 24 hour record of the 63 year old technician with emphysema Values were not obtained for 2 hours because of a technical problem which was corrected Considerable physical activity is noted chiefly walking both at work and at home While awake his over all mean pressure was 123/67 and mean heart rate 78 During 6 5 hours of restful sleep at home his

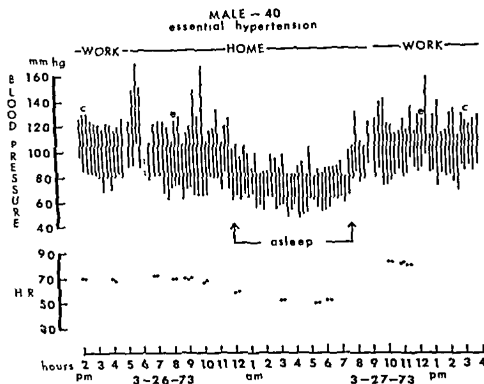


Fig 4 A 26 hour record of blood pressures and heart rates at 15 minute intervals obtained from a 40-year-old pharmacologist with essential hypertension who was receiving hydrodiuril therapy The highest pressures were recorded at physical rest while conv rsing with associates relating to his work

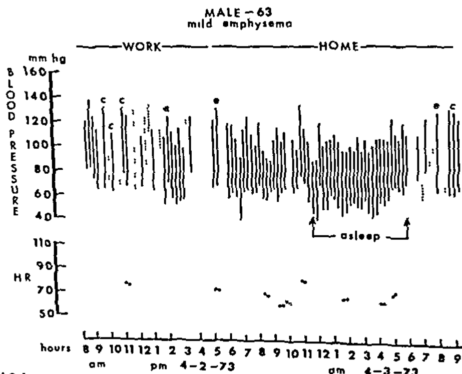


Fig 5 A 24 hour recording of blood pressures and heart rates at 15 minute intervals for a 63-year old laboratory technician who had mild emphysema. He was not taking any medications

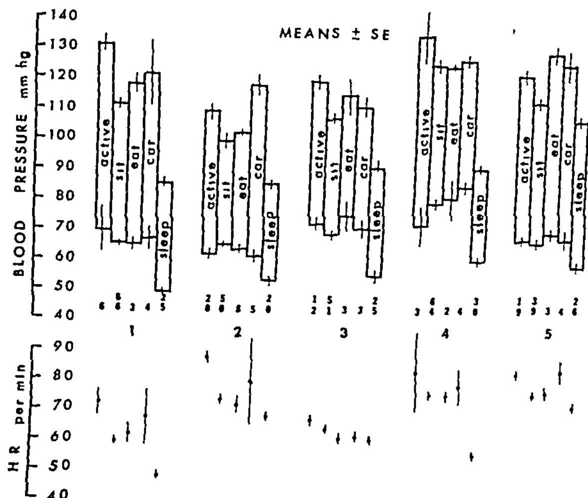


Fig 6 Means and S F for systolic and diastolic blood pressures (histograms) and for heart rates (solid dots) for each of the five subjects for each of the five circumstances indicated The figures under each histogram represent the number of measurements in each instance

pressures averaged 107/57 and heart rates 70, which was in contrast to the greater decreases in both variables seen in the other four subjects There was very little variability of pressure but some variability in rate during sleep With physical activity there were modest increases, in most instances in systolic pressures only Eating was accompanied in the three instances by increases in systolic pressure but without change in rate A modest increase occurred in systolic values during car driving

Mean values under five circumstances for the five subjects Fig 6 shows for each of the five subjects the means ± standard error for all data arranged according to involvement which included active (chiefly walking) 'sit eat' car (driving) and sleep' The figures below each bar represent the number of values for each type of involvement

While physically inactive (sit), the pressures are quite similar for the first three subjects, somewhat higher for the hypertensive (Subject 4), and a wider pulse pressure in Subject 5 Using 'sit as a point of reference, the following may be said for all five subjects Elevated systolic values in all five subjects were associated as would be expected with physical activity Diastolic values failed to show a pattern with two increasing two decreasing and one not changing Heart rates were accelerated as anticipated, in all subjects with the least increase seen in Subject 3 who was taking propranolol Eating was associated with modest systolic elevations in four of the five subjects and with variable diastolic changes with three increasing one decreasing and one showing no change Heart rates were unchanged in two decreased in two and increased slightly in one With respect to car driving systolic pressures rose in all subjects and diastolic values increased in four and decreased in one Accompanying heart rates increased in four but decreased somewhat in the subject taking propranolol During sleep systolic and diastolic pressures decreased significantly in all five subjects, and heart rates similarly decreased in all, but more markedly so in Subjects 1 and 4

Discussion

Perhaps the most important finding was the fact that it was not only possible but quite feasible to obtain recordings of indirect blood pressure and heart rates in subjects who go about their usual activities at work and while at home including sleep there All of the subjects had worn the device from three to 10 times before for 8 hour periods during their usual work day so that the experience during the 24 hour recording was neither a unique nor a novel experience for them The identification of type of involvement depends on the accuracy of the dictated diary information This appeared to be quite satisfactory in these five subjects but may be a problem for those wearing the recorder for the first time Activity values are recorded with the subject stopping his physical activity and holding the arm still Should the subject continue his activity artifacts often result and preclude an accurate reading of the record The values obtained however appear to reflect the activity even though the values might have been somewhat higher had the subject continued to exert during the recording None of the subjects was involved in unusual physical activity at his work which probably accounts for the relatively modest increases in pressure during activity

The modest elevation in systolic pressure during eating observed in four of the five subjects is not surprising since increased cardiac work has long been identified with eating and digestion Increases in pressure while driving a car might be expected and were identified here but they were not marked Such increases undoubtedly are related to circumstances under which the driving is done (heavy traffic high temperature etc) and probably to the emotional state of the driver at the time

Of interest is the fact that for all five subjects pressures or heart rates or both were higher during the first 3 to 5 hours after awakening in the morning than for the rest of the day The explanation for this observation is unknown and one can only speculate as to whether this represents a "rebound" phenomenon after sleep or is somehow related to the well known diurnal rhythm of corticosteroid levels

Of special interest are the sleep values which are unique since they were obtained during sleep at home automatically Pressures and rates have been extensively studied in sleep laboratories and hemodynamic studies have shown that pressures follow the level of sleep and that the mechanism appears to be that of a progressive decrease in peripheral resistance and on other occasions to a decrease in cardiac output [3] Since electroencephalograms were not obtained it is not possible to relate variations in pressures and rates in our subjects to sleep level or to periods of rapid eye movement sleep as reported in several sleep laboratory studies The lack of variability in pressures in Subject 1 may be related to the diazepam taken 30 minutes prior to sleep The lack of major decreases in pressure in Subject 2 may be related to his restlessness The marked variability of pressures in the subject with the prior myocardial infarction and angina is of great interest but not explainable The hypertensive man s considerable fall in pressure during sleep is consistent with similar observations of others [2, 4, 6] The sustained pressures and rates in the elderly subject with emphysema (Subject 5) suggest that more cardiac work is being performed during sleep in him than in the other subjects

Summary

It proved feasible and practical to automatically record indirect blood pressure at 15 minute intervals with a 4 pound portable device throughout a 24 hour period in five subjects at work and at home awake and asleep Of the subjects two were apparently healthy and three had coronary artery disease mild essential hypertension and emphysema respectively Most striking was the hypotension accompanying sleep which was greatest in the hypertensive subject and least in the subject with emphysema Activity while mainly walking resulted in only modest changes in pressure There was a tendency toward slight pressure rises associated with eating and modest tachycardia while driving a car There was a tendency in all five subjects to exhibit somewhat higher pressures during the first 4 to 5 hours after awakening

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Metabolic and cardiovascular abnormalities in patients with peripheral arterial disease

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In contrast to ischemic heart disease little is known about possible metabolic and cardiovascular abnormalities in patients suffering from intermittent claudication occurring as a result of underlying peripheral arterial disease Previous studies of patients with lower limb arterial disease have suggested that 97 5 per cent of them smoked and the serum cholesterol level was abnormally high if the patients were nondiabetic While there is good evidence that diabetes mellitus increases the prevalence and severity of arteriosclerosis obliterans Schadt and his colleagues found co-existing diabetes mellitus in only 15 per cent of their patients with atherosclerotic occlusions of the femoral artery Evidence that hypertension is an important factor in the pathogenesis of arteriosclerosis obliterans is not well documented although Juergens and his co workers[1] have suggested that blood pressure levels in excess of 150/90 mm Hg occur in about one quarter of patients with symptomatic lower limb arterial disease against an expected incidence of about 10 per cent

Thus, while some reports suggest that peripheral arterial disease may be associated with some of the risk factors which operate in cerebrovascular and ischemic heart disease it s interrelationship with smoking disturbed glucose tolerance hyperlipoproteinemia and concomitant cardiovascular abnormalities is in need of greater study

Hence a study was undertaken of 28 patients with severe peripheral arterial disease and 28 control subjects in order to define further any metabolic abnormalities in this type of patient Since it has been reported that all of 15 patients with Buerger s disease had an elevated serum copper level[3] the relationship of the anomaly in patients with peripheral arterial disease was also studied

Methods

Twenty-eight consecutive patients of an average age of 63 years (range 43 to 84 years) with arterial disease who attended the Peripheral Vascular Out Patient Department of Cedars Sinai Medical Center were studied All 28 patients had severe symptoms of lower limb claudication of over 1 year s duration so that the limit of walking in all cases was two blocks of ambulation The pain of claudication was always relieved after several minutes of rest In all patients the diagnosis was confirmed by standard vascular studies with a 4 limb pneumatic plethysmograph (Electrodiagnostic Instruments Burbank Calif) and temperature measuring equipment (Leeds and Northrup Speedomax Recorder

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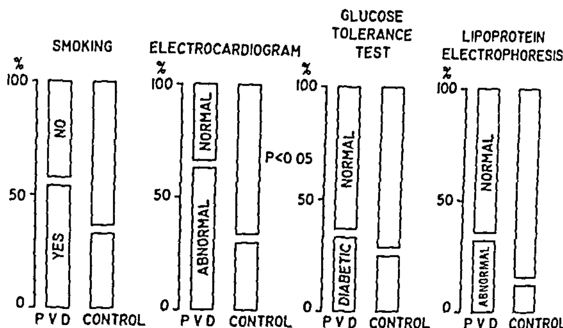


Fig 1 This figure shows the incidence of smoking ECG abnormalities abnormal glucose tolerance tests and abnormal lipoprotein electrophoresis in patients with peripheral vascular disease (*PVD*) and control subjects (control) The incidence of smoking abnormal glucose tolerance and hyperlipoproteinemia tend to be greater in PVD patients compared to control subjects but the difference was not statistically significant The incidence of ECG abnormalities in PVD is significantly greater than seen in the control subjects ($p < 0\ 05$)

Monterey Park, Calif)[4, 5] Translumbar arteriography was also performed in those patients considered suitable for surgical repair

A further 28 patients of an average age of 59 years (range, 28 to 80) and suffering from leg pain acted as a control series The cause of the leg pain in all the control patients was degenerative joint disease of the lumbar spine causing sciatic nerve compression and radiation of pain to the lower limb as confirmed by electromyelography and x rays of the lumbar spine In addition, all 28 control patients underwent standard plethysmographic vascular examination and no evidence of peripheral vascular disease (PVD) was found

All 56 patients underwent the following investigations A standard 12 lead electrocardiogram (ECG) a 5 hour glucose tolerance test (100 Gm of glucose orally) fasting serum cholesterol, fasting serum triglycerides, serum copper hematocrit determination and lipoprotein phenotyping by electrophoresis These tests were performed as a standard laboratory investigation according to the protocols of the Division of Laboratories and Biochemistry of Cedars Sinai Medical Center All patients were prepared for several days with a high carbohydrate intake prior to testing or glucose tolerance, and were fasted for 14 hours prior to lipoprotein measurements The glucose tolerance tests were interpreted according to the criteria of Andres[4] No patients were receiving estrogen type compounds Brachial arterial blood pressure was determined by auscultation

Statistical evaluation of the results was obtained with multivariant analysis and the Fisher Exact Test for contingency tables Data relating to incidence of smoking ECG abnormalities, lipoprotein, and glucose tolerance were compared with the chi square test, differences in serum cholesterol, triglycerides copper, and hematocrit were examined by Student s t test

Results

Twenty-eight patients with PVD were studied and the results compared with a similar number of control patients who suffered leg pain but were free of vascular disease

Smoking Fifteen PVD patients had smoked at least five cigarettes daily in the five years prior to the study (Fig 1) This was a higher prevalence than seen in the control series, in which nine patients smoked but the difference was not statistically significant

Cardiovascular abnormalities Sixteen PVD patients showed ECG abnormalities The most common abnormality seen was evidence of left ventricular hypertrophy which occurred in nine patients In seven patients there was evidence of an old myocardial infarction Two patients had a bundle branch block pattern (Fig 2)

The incidence of ECG abnormalities was great

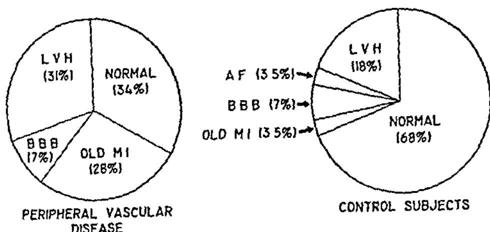


Fig 2 The incidence of ECG abnormalities in patients with peripheral vascular disease (PVD) and control subjects. The incidence of ECG abnormalities is greater in PVD particularly in the number of patients who show evidence of left ventricular hypertrophy and an old myocardial infarction Abbreviations *MI* = myocardial infarction, *LVH* = left ventricular hypertrophy *BBB* = bundle branch block, *AF* = atrial fibrillation

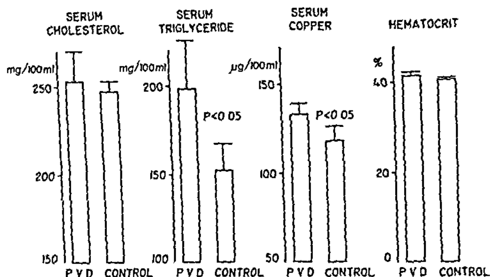


Fig 3 The level of serum cholesterol, serum triglycerides serum copper and hematocrit in patients with peripheral vascular disease (PVD) and control subjects (control) Mean serum triglycerides and copper determinations are higher in PVD patients ($p < 0.05$) Mean serum cholesterol and hematocrit levels in PVD patients are most identical with those found in control subjects (mean ± S E M)

er than that seen in the control subjects ($p < 0.05$) (Fig 1) In two thirds of the control group the ECG was normal Of the remaining subjects, five had evidence of left ventricular hypertrophy and one each had evidence of an old myocardial infarction atrial fibrillation and two patients had bundle branch block

In PVD patients mean cuff brachial diastolic blood pressure was 88 mm Hg with eight patients having diastolic pressures of 100 mm Hg or greater This reading was higher than in control patients, in whom diastolic pressure averaged 83 mm Hg ($p < 0.05$) Similarly, mean brachial systolic blood pressure of 156 mm Hg was higher in PVD patients than the control reading of 144 mm Hg ($p < 0.05$) In all 18 of the 28 PVD patients were hypertensive (systolic pressure of 150 mm Hg or greater diastolic pressure of 90 mm Hg or greater)

Metabolic abnormalities The glucose tolerance test[4] was abnormal in eight PVD patients which was not significantly different from the six abnormal tests found in the control group (Fig 1)

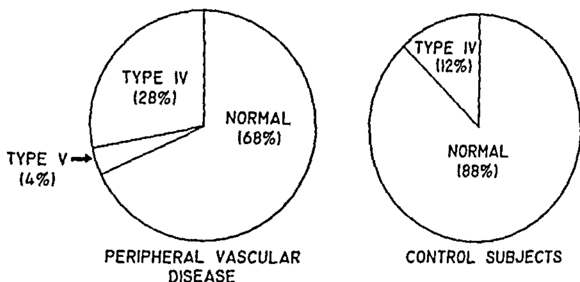


Fig 4 The incidence of lipoprotein abnormalities in patients with peripheral vascular disease and control subjects. A higher incidence of lipoprotein abnormalities is seen in patients with peripheral vascular disease (32 per cent) when compared to control subjects (12 per cent)

Mean serum cholesterol level was 252 mg per 100 ml in PVD patients, in control subjects the average level was 247 mg per 100 ml When these values were compared to the normal range adjusted for age,[7] only one PVD patient had an abnormally high serum cholesterol value, which was identical to one subject seen in the control group

In contradistinction, mean serum triglyceride levels showed a marked contrast between the two groups of patients In PVD patients mean serum triglyceride level was 198 mg per 100 ml, which was higher than the level of 151 mg per 100 ml ($p < 0.025$) seen in the control group (Fig 3) When these values were compared to the normal range adjusted for age, exactly half of the PVD patients had abnormally higher serum triglyceride levels, in contrast to five abnormal readings in the normal group Type IV hyperlipoproteinemia was found in seven and Type V in one PVD patient In the control group Type IV was found in only three subjects (Fig 4) The presence of Type IV hyperlipoproteinemia showed a positive correlation with increased serum triglyceride levels Hematocrit levels were nearly identical in both groups of subjects (Fig 3)

Statistical examination by multivariant analysis showed a significant correlation ($p < 0.01$) between a diabetic glucose tolerance test, elevated triglycerides hyperlipoproteinemia, and high hematocrit levels

Serum copper levels were elevated in seven of the 28 PVD patients The average level of 133 µg per 100 ml in PVD patients was higher than the mean value of 118 µg per 100 ml seen in control subjects ($p < 0.05$) Analysis showed a statistical relationship ($p < 0.05$) between an elevation of serum copper levels and a history of current cigarette smoking An elevated serum copper level was not related to any other of the variables examined

Discussion

The natural history of peripheral vascular disease needs to be better understood One important reason for this is that, while symptoms and signs of peripheral arterial disease usually become manifest late in life, significant impairment of limb flow is often detectable for a decade or more before the onset of symptoms[8] Another reason for the further need for identification of factors which may be contributing to the development of peripheral vascular disease is the relative accessibility of the peripheral vessels for diagnostic study which may allow the early identification of patients with asymptomatic arteriosclerotic disease before the more serious consequenes of the same disease process involve the myocardium or central nervous system In the present study the number of patients studied is small by some standards, but analysis of the results obtained shows that the correlative trends are strong and that the further enlargement of the series by a doubling or tripling of the number of patients studied does not appear to be justified

The Framingham study showed an increased risk of intermittent claudication in patients with angina and coronary heart disease suggesting a

common underlying basis for claudication and coronary disease[9] This study showed that the principal hazard for subjects with claudication appeared to derive from an increased propensity to cardiovascular morbidity and death rather than from the consequences of impaired circulation to the limb

These findings are again supported in the present study in that whereas the mean cuff brachial diastolic blood pressure was 88 mm Hg which may be normal for this age group eight of the 28 PVD patients had brachial diastolic pressures of 100 mm Hg or greater In all 18 of the 28 PVD patients were hypertensive (brachial systolic pressure of 150 mm Hg or greater diastolic pressure of 90 mm Hg or greater) This is in contrast to the study of Juergens and his colleagues who found this level of blood pressure in only 25 per cent of patients with lower limb arterial disease

Patients with arterial disease of the legs usually have lower blood pressure in the legs than in the arms, which may be related to the stenotic pressures in their lower limbs but further investigation into the responsible mechanisms is needed

The incidence of ECG abnormality encountered was 63 per cent with seven patients showing evidence of an old myocardial infarction While no direct relationship was seen between diastolic pressure levels and the type of ECG abnormalities detected 25 of 28 PVD patients (89 per cent) had either an ECG abnormality or a cuff pressure of 90 mm Hg or greater This incidence was greater than the finding of the same abnormalities in 19 of the 28 control subjects ($p < 0.05$)

Since this incidence of cardiovascular abnormalities is so high it appears essential that a patient presenting symptomatology of PVD must be thoroughly examined for other signs of abnormality in the cardiovascular system This would be particularly important if major peripheral vascular surgery is contemplated

The high incidence of multisystem illnesses in patients with PVD is again demonstrated if metabolic abnormalities are considered Twenty one of twenty-eight PVD patients (75 per cent) had metabolic abnormalities If both cardiovascular and metabolic abnormalities are considered then 26 of 28 PVD patients (93 per cent) had abnormalities in addition to their PVD

In the present study there exists a strong correlation between abnormalities of glucose tolerance elevated triglycerides and hyperlipoproteinemia as is also commonly encountered in patients with coronary heart disease The most common disturbance of hyperlipoproteinemia encountered was of the pre beta type IV which confirms the findings of Greenhalgh and colleagues[10] with respect to PVD An interesting negative finding in this group of patients with profound atherosclerotic vascular disease is that at the time of measurement the serum cholesterol level was elevated in only one of them This is in contrast to the earlier study of Juergens and co workers[1] who found that in a series of nondiabetic patients with arteriosclerosis obliterans mean cholesterol level was 50 mg per 100 ml higher than that of the control patients In the present study the mean cholesterol level of the nondiabetic patients was 244 mg per 100 ml which was nearly identical to that of the present control series

Juergens also found in his study the incidence of smoking to be 97.5 per cent whereas in the present study only 15 of the 28 patients smoked When other factors known to predispose to accelerated vascular disease (such as smoking the presence of hypertension diabetes mellitus or hyperlipidemia) are considered then every patient in the present study had such a risk factor evident with the majority of them having two or more risk factors present

Khandekar and co workers[3] have reported that 100 per cent of the patients with Buerger s disease had elevated serum copper levels and the suggestion has been made by others that possibly this abnormality may be useful as a screening test for PVD In this study a positive correlation ($p < 0.05$) was found between a history of current smoking and an abnormally high serum copper level. No relationship was found between serum copper and any other of the measurements obtained in this group of patients The fact that serum copper was normal in 21 of the 28 PVD patients (75 per cent) suggests that an estimation of serum copper used routinely as a screening test for arteriosclerotic PVD is not indicated Whether or not this test would be of value in differentiating Buerger s disease from nonsmoking patients with arteriosclerotic PVD needs to be determined

Summary

Twenty-eight consecutive patients of an average age of 63 years with intermittent claudication secondary to underlying peripheral arterial

disease were studied for evidence of metabolic or other cardiovascular abnormalities and the results obtained were compared with those of 28 matched control subjects free of vascular disease

Patients with peripheral arterial disease had significantly higher levels of systolic and diastolic blood pressure, a greater incidence of ECG abnormalities lipoprotein abnormalities, elevated serum triglycerides, and serum copper The incidence of smoking and abnormal glucose tolerance, while higher in peripheral arterial disease patients was not statistically significant Hematocrit and serum cholesterol levels were nearly identical in both groups of patients

Twenty six of the 28 patiens with peripheral arterial disease had either a cardiovascular or a metabolic abnormality, indicating the high incidence of multisystem illness in this disorder The epidemiologic data in peripheral arterial disease are similar to those in coronary artery disease but some measurements contrast sharply, such as the apparent normal level of serum cholesterol in patients with peripheral arterial disease

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Acute bacterial percarditis in children
Report of 25 cases

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Acute bacterial pericarditis with effusion is a rare complication of primary bacterial infection in children and is usually fatal if misdiagnosed or improperly treated Several reports have dealt with experiences involving small numbers of pediatric patients[1-5] The purpose of this paper is to present 25 cases seen at the Children s Hospital National Medical Center during the years 1962 through 1973 This represents the largest published series from a single institution

Methods and materials

The hospital records of all patients with proved diagnosis of bacterial pericarditis were reviewed The charts of the patients who survived and the autopsy records of those patients who died were reviewed with particular attention to the prodromal period symptoms and physical findings on admission to the hospital associated illness bacteriology and the outcome of therapy especially as related to the mode of treatment Available electrocardiograms (ECG) and chest x rays were also reviewed

Results

Between 1962 and 1973 25 patients with purulent pericarditis were seen at this institution (Table I) Ages ranged from 5 months to 14 years Ten (40 per cent) were 2 years of age or younger and 15 (60 per cent) were under 5 years of age Thirteen (52 per cent) of the patients died

Associated illness Associated illnesses were present in 24 (96 per cent) of the cases (Table II) Most commonly encountered associated illnesses were respiratory tract infections in 15 meningitis in five leukemia in two and sickle cell anemia in two There was one each of osteomyelitis burn and impetigo

Symptoms Table III lists the common symptoms in our patients The duration of symptoms until presentation to the hospital ranged from one to 21 days The average duration was 5 days Fever was present in 64 per cent Chest pain seen commonly in older children and adults[6,7] was seen only in four (16 per cent) of our cases

Physical findings The findings on physical examination are summarized in Table IV Tachycardia tachypnea and signs of congestive heart failure were most commonly found A pericardial friction rub pathognomonic of pericarditis[8] was present in only five of our patients on admission and subsequently appeared in three others during hospitalization Pulsus paradoxus was observed in six yet 19 of the 25 had significant effusion or tamponade

Bacteriology Positive bacterial cultures were obtained in 19 (76 per cent) of the 25 patients In the remaining six although significant purulent fluid was recovered from the pericardial space no organisms were isolated Although Van Reken and associates questioned the wisdom of including such patients we feel that therapy prior to admission is largely responsible for such sterile cultures Table V lists the organisms recovered and the outcome of the patients *Staphylococcus aureus Hemophilus influenzae* type B and

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Table 1 Clinical summary

Pt no	Year	Patient	Age	Associated illness	Organism	Rx prior to admission	Hospital therapy*	Outcome and comment
1	1962	T H	6 mo	Sickle cell disease	–	–	S	Died 16 hr after admission
2	1963	M S	5 yr	Second and third degree burns	*Staphylococcus aureus*	–	C	Died 100 ml. of pericardial fluid at autopsy
3	1964	G M	14 yr	Down s syndrome URI	–	Gantrisin Penicillin	M	Died 500 ml of fluid in pericardial space
4	1965	V P	3 yr	Leukemia	*E coli*	Penicillin chloramphenicol	M	Died
5	1966	D P	5 mo	Bilateral pneumonia	Klebsiella from pericardial fluid *E coli* from lung and pericardial fluid	Digitalis	M	Died 45 c c of thick purulent fluid at autopsy
6	1966	C T	9 yr	Sickle cell disease	Klebsiella from blood lung and left ear	–	N	Died moribund on admission
7	1966	K N	3 yr	Severe bilateral pneumonia	*Hemophilus influenzae* type B	–	N	Died
8	1966	O Y	1 yr	Pneumonia meningitis	Pneumococcus	–	N	Died (DOA) located fluid in pericardial space
9	1967	C W	15 mo	Acute lymphocytic leukemia URI	*S aureus*	–	M	Died
10	1967	G M	7 yr	Pharyngitis cervical adenitis	–	Prostaphilin erythromycin oral penicillin	N	Died (DOA) 450 ml. of purulent fluid at autopsy
11	1967	T K	11 yr	Meningitis	Meningococcus	Ampicillin	C	Survived developed constrictive pericarditis
12	1967	E K.	7 yr	Pharyngitis pneumonia	Pneumococcus	Achromycin	M	Survived
13	1967	D R	10 yr	Pharyngitis	–	Penicillin	M	Survived
14	1968	F M	11½ mo	Meningococcemia URI	?/Meningococcus	Intramuscular penicillin ampicillin	M	Died
15	1968	H B	20 mo	FUO	–	Ampicillin	M	Died 400 c c of purulent fluid
16	1968	D T	7 yr	Impetigo	Beta hemolytic streptococcus	Ampicillin kanamycin oxacillin penicillin	C	Survived
17	1968	D T	6 yr	Meningitis	Meningococcus	–	M	Survived
18	1969	P V	3 yr	Meningitis RLL pneumonia	*H influenzae* type B	Penicillin ampicillin	M	Died moribund on admission
19	1969	T S	23 mo	–	*S aureus*	–	C	Survived
20	1969	L. W	4 yr	Pharyngitis	–	Penicillin 7 days PTA	C	Survived
21	1970	J Q	2 yr	Pneumonia	*S aureus*	–	C	Survived
22	1970	G W	13 yr	Meningitis	Meningococcus	–	C	Survived
23	1971	S F	10 mo	Pneumonia otitis media	*H influenzae* type B	–	C	Survived
24	1972	T H	6 yr	Osteomyelitis pneumonia	*S aureus*	–	C	Survived
25	1973	R M	9 mo	Otitis media	*H influenzae* type B	–	C	Survived

*N no therapy M medical therapy alone S surgical therapy alone C combined medical and surgical therapy URI upper respiratory tract infection FUO fever of undetermined origin Rx treatment DOA dead on arrival PTA prior to admission

Table II Associated illness in 25 patients

	No of patients
Pharyngitis	6
Pneumonia	[illegible]
Meningitis	5
Otitis media	4
Anemia	3
Impetigo	1

Table III Symptoms noted on admission of the patients

	No of patients
Fever	16
Upper respiratory infections	8
Anorexia	6
Chest pain	4
Cough	3
Abdominal pain	3

meningococcus were the most frequently recovered organisms

Meningococcus was recovered in four patients Two of the three patients who survived meningococcal pericarditis Patient 11 and 17 have already been reported from this institution [8] The one patient who died was an 11½ month old boy who had the clinical syndrome of meningococcemia with gram negative diplococci seen on the smear of a petechia He had received an intramuscular injection of penicillin prior to being brought to the hospital At autopsy examination 30 ml of purulent fluid were aspirated from the pericardial sac but cultures were sterile

The gram negative organisms *E coli* and Klebsiella were recovered in four patients Patient 5 a 5 month old infant died from gram negative sepsis *E coli* and Klebsiella were cultured from the pericardial fluid and *E coli* from the lungs The other two patients from who gram negative organisms were recovered had diseases known to predispose patients to overwhelming gram negative infections i e leukemia and sickle cell anemia Acute cardiac tamponade was responsible for the death of all three patients

ECG ECG s were available for analysis in 12 of the 25 patients All 12 patients had abnormal ST T segments on their initial tracings Eleven of the 12 tracings demonstrated ST segment elevation (Fig 1) and one had ST segment depression All ST segment abnormalities became normal

Table IV Physical findings in 25 children with purulent pericarditis

	No of patients
Tachycardia	17
Tachypnea	12
Signs of congestive heart failure	11
Pericardial friction rub	
On admission	5
Subsequently	3
Pulsus paradoxus	6

Table V Bacteriology and outcome of the patients

Organism	*Total no of patients*	*No that survived*
S aureus	4	2
Hemophilus influenzae type B	4	2
Meningococcus	4	3
Pneumococcus	2	1
Beta hemolytic streptococcus	1	1
Gram negative organisms	4	0
Sterile culture	6	2

Two organisms were cultured from the same patient (see text)

within 2 to 3 days after institution of therapy Only three patients had abnormally low voltages in their ECG s Following recovery one of these three had borderline voltage criteria for left ventricular hypertrophy but 1 year after the acute illness the ECG was normal

Chest roentgenograms Chest roentgenograms were available for review in 18 of the 25 patients All 18 showed moderate to severe cardiomegaly with the cardiothoracic ratio ranging from 58 to 86 per cent The heart appeared globular and the lung fields were normal in most of the films except in those with intercurrent pneumonic infiltrates Fig 2 is representative of the group

Treatment and results Table VI summarizes the results of treatment of the 25 children Survival rates were best in 10 patients who received both medical (i e antibiotics) and surgical (i.e pericardiocentesis and/or pericardectomy) therapy The only patient who did not survive combined therapy was 5 year old Patient 2, with infection from *S aureus* complicating extensive second and third degree burns Seven of 10 patients treated medically without surgical drainage died as did the one patient who received surgical drainage alone All four untreated patients died Patient 11 developed constrictive

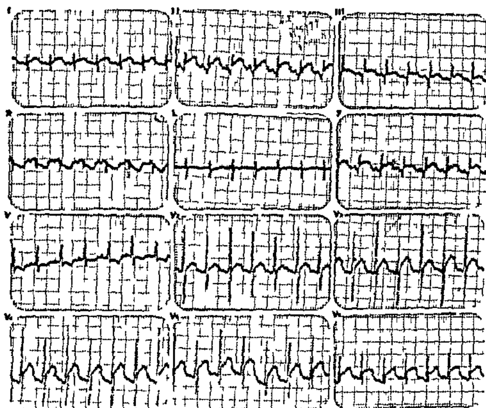


Fig 1 The ECG of Patient 25 on admission showing ST T segment elevation characteristic of pericarditis Note normal voltage in all leads



Fig 2 The admission AP roentgenograph of Patient 23 demonstrating cardiomegaly normal pulmonary vasculature and left lower lobe pneumonia

pericarditis within 1 month following acute meningococcal pericarditis and was successfully treated with pericardectomy[8]

Comment

Purulent bacterial pericarditis is encountered infrequently in childhood In previous studies it was found to occur primarily in children under 2 years of age[1,3,4,9] In our experience, however, only 40 per cent of these cases were seen in this age group

Table VI Mode of treatment and outcome

Mode of therapy	*No of patients*	*No that survived*	*No that died*
No treatment	4	0	4
Medical treatment alone	10	3	7
Surgical treatment alone	1	0	1
Combined medical and surgical treatment	10	9	1
Total	2,	12	13

Mortality rates are high in all age groups Several factors should be mentioned in discussing the high mortality rates here First early recognition diagnosis and institution of proper therapy are mandatory to prevent death from cardiac tamponade Three of the four patients who received no treatment were admitted moribund Second, it should be noted (see Table I) that from 1962 to 1967 the mortality rate from this disease at our institution was 77 per cent (10/13), whereas from 1968 to 1973 only 25 per cent (3/12) have died We feel that this improvement relates in part to earlier recognition and treatment

The presence of a pericardial friction rub clearly points to pericardial involvement and this

was present in only six patients when initially examined The most reliable information is obtained from radiologic examination of the chest The presence of a large cardiac silhouette with normal pulmonary vasculature in a child with fever should immediately raise the question of pericardial effusion (Fig 2) This was noted in all 18 available chest roentgenograms When associated with fever tachypnea tachycardia and signs of circulatory congestion with or without pulsus paradoxus immediate steps should be taken to rule out pericardial effusion (An abnormal pulsus paradoxus is the inspiratory decrease in the systolic pressure of 10 mm Hg or more that may result from pericardial compres sion pulmonary emphysema or congestive heart failure)

In the less critically ill child angiography technicium scanning and echocardiography are reliable methods of diagnosing a pericardial effu sion In the critically ill child however a subdiaphragmatic pericardiocentesis from the xiphisternal angle can be performed safely and rapidly This procedure not only determines the presence and nature of an effusion but also initiates therapy by establishing drainage and decompression of the pericardial space

It has become apparent that survival from purulent pericarditis is dependent upon the mode of therapy In our experience only three out of 10 (30 per cent) children treated with antibiotic therapy alone survived whereas nine of 10 (90 per cent) survived with combined antibiotic therapy and surgical drainage of the pericardial space Since 1969 we have had no deaths from purulent pericarditis treated in this manner

On the basis of our experience and that of others [1] it is recommended that combined antibiotic therapy and surgical drainage is the treatment of choice in managing the child with acute bacterial pericarditis Intravenous route of administration of appropriate antibiotics is neces sary to achieve adequate blood levels and therapy should be continued for 2 to 4 weeks depending on the clinical response The institu tion of adequate surgical drainage is the key to successful therapy At times diagnostic pericar diocentesis with removal of the pericardial fluid is sufficient for adequate drainage More often it is necessary to perform thoracotomy with place ment of drains through a pericardial window to achieve adequate drainage The length of the time during which the drains are left in place is of course dependent on need and has average 4 to 5 days in our patients who have survived

Finally although pericardial constriction infre quently occurs [5, 8] all patients should be followed carefully for this complication When present pericardectomy is indicated and may be life saving

Summary

Twenty five patients aged 5 months to 14 years with acute bacterial pericarditis are reported Thirteen (52 per cent) of the patients died The presenting symptoms associated illness and physical findings bacteriology and response to therapy are reviewed Optimum therapy consists of intravenous administration of specific antibiotics combined with surgical drainage 90 per cent of our patients treated in this fashion survived Antibiotic therapy alone is usually inad equate especially in the presence of significant effusion and among our patients only three of 10 patients so treated survived One patient devel oped constrictive pericarditis 1 month after the initial attack with meningococcal pericarditis and required pericardectomy

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Amplitude of the first heart sound at rest and during exercise in normal subjects and in patients with coronary heart disease

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The intensity of the first heart sound (S_1) is decreased at rest in conditions associated with left ventricular dysfunction A faint, muffled first heart sound is a common physical finding in myocardial infarction, and a decreased intensity with loss of high frequency components has recently been documented in careful quantitative phonocardiographic studies[1, 2] during the acute phase It has also been demonstrated that the peak rate of rise in left ventricular pressure is an important determinant of the amplitude of S_1[3, 5] Exercise augments the peak rate of rise in left ventricular pressure (peak LV dp/dt) and S_1 intensity in normal subjects Myocardial ischemia decreases the velocity of fiber shortening and LV dp/dt[6, 7] An ischemic ventricle would be expected to generate a lower peak LV dp/dt during stress than a normal ventricle, and this should be reflected by an attenuated S_1 amplitude response

The purpose of the present investigation was to compare the effect of exercise on S_1 amplitude in normal subjects with that in patients who had documented coronary heart disease

Methods

Twenty two patients with at least one major coronary artery (left main, anterior descending, circumflex, or right coronary artery) demonstrating a 50 per cent reduction of vessel diameter on coronary angiography were included Ten of the patients had suffered at least one myocardial infarction in the past One patient had one vessel disease, 11 had two vessel, and 10 had three vessel disease Seven patients had a normal left ventricular angiogram The remainder had either localized or generalized abnormalities of wall motion No patient had evidence of recent myocardial infarction, valvular dysfunction, primary myocardiopathy, or elevated arterial pressure at rest All patients were taking nitroglycerin and/or long acting nitrates for angina No patient was on beta blocking agents at the time of this study Three were on digitalis Except for an occasional premature ventricular contraction, no arrhythmias were noted during an observation period of 10 minutes before exercise testing

The control group consisted of 32 men who were studied before entering various physical training programs The mean age was 36 3 years, with a range from 17 to 56, 18 subjects were 39 or younger, and 14 were 40 or older History and physical examination were in each case negative with respect to cardiovascular disease, including resting arterial blood pressure below 150/95 mm Hg All control subjects had a normal ECG at rest and a normal ECG response to exercise

All subjects and patients performed progressively heavier bicycle exercise in the upright position The initial work load and the load increment were 300 kilopond meter (k p m) per minute in normal subjects and 150 or 300 k p m

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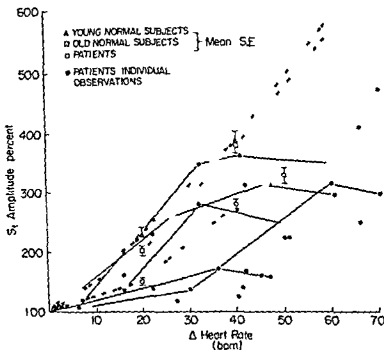


Fig 1 Relationship between change in S_1 amplitude and change in heart rate in normal subjects and in patients with coronary disease Mean data for young (n = 18) and old (n = 14) normal subjects and patients with coronary disease (n = 22) S_1 amplitudes during exercise are measured as per cent of the individual amplitude at rest ΔHeart rate denotes the heart rate increase in beats per minute above resting level. Solid lines connect data points from 5 individual patients who demonstrated a decrease in S_1 amplitude coinciding with the onset of angina pectoris.

per minute in patients (depending on clinical history and the response to exercise during the test) The duration of exercise was 5 minutes at each load with rest periods of equal duration interspersed between loads The target level was maximal oxygen uptake but the test was terminated prior to this end point if the patient developed angina pectoris significant (at least 1 mm horizontal or downward sloping) progressive S-T segment depression increasing ventricular irritability (with more than 1/10 beats a ventricular premature contraction) or falling systolic arterial pressure

A modified Frank lead vectorcardiogram (VCG)[4] blood pressure respiratory rate and phonocardiogram were recorded at rest and during the last 30 seconds of exercise at each load The phonocardiographic (PCG) instrumentation consisted of an Elema EMT 25B (Siemens) piezoelectric accelerometer microphone (weight 20 grams) coupled to multiple electronic band filters. The range selected for analysis had a 100 Hz center frequency with a 12-db per octave symmetrical attenuation. Placement of the microphone was uniformly in the fourth intercostal space immediately to the left of the sternal border The microphone was attached to the chest wall with double faced tape The VCG and PCG were recorded on an FM analog tape recorder at 7 5 i p.s with a frequency response ±6 db over the range DC to 1,250 c p.s For analysis the data were replayed onto an Elema Mingograf 81 (Siemens) ink jet recorder at a paper speed of 100 mm per second The frequency response of this instrument is within 3 db over the range from DC to 600 Hz

At rest and during each progressive steady state exercise load a sequence of 10 consecutive beats was selected randomly Maximal peak to peak S_1 amplitudes were measured and averaged S_1 amplitudes during exercise were normalized with respect to individual resting S_1 amplitudes S_1 amplitudes during exercise were expressed as percentages of the amplitude at rest No attempt was made to evaluate absolute amplitudes Changes in S_1 amplitude during exercise were related to changes in heart rate from sitting rest in order to provide a frame of reference independent of individual variations in physical performance capacity and related to relative level of

Table I Mean data at rest and during exercise in normal subjects and in patients with coronary heart disease

Group		Rest				ΔHR = 20					ΔHR = 40				
		HR	SBP	DBP	S	HR	WL	SBP	DBP	S	HR	WL	SBP	DBP	S
Young normals	Mean	67	113	73	100	84	225	127	74	207	107	422	144	76	380
(n = 18)	S E	2 0	2 4	2 7			17	2 4	2 1	16 3		26	3 3	2 5	35 6
Old normals	Mean	72	119	77	100	92	289	140	81	229	112	540	162	83	38[illegible]
(n = 14)	S E	2 2	5 2	4 6			23	6 7	4 2	21 1		33	7 7	4 8	35
p diff							< 0 05					< 0 01			
Combined normal group	Mean	69	116	74	100	89	252	133	77	216	109	472	151	80	381
(n = 32)	S E	1 6	2 7	2 5		1 7	15	3 5	2 2	13 0	1 7	23	4.2	2 6	24 9
Patients	Mean	78	118	76	100	98	221	139	80	156	116	403	148	83	[illegible]95
(n = 22)	S E	2 6	3 0	2 0		2 9	24	4 0	2 4	8 1	3 1	32	4 5	2 8	2[illegible]0
p diff †		< 0 01	< 0 01			< 0 05				< 0 01	< 0 05				< 0 01

p value for the difference between young and old normal subjects
†p value for the difference between the combined normal group and patients with arteriosclerotic heart disease
Abbreviations HR = heart rate beats per minute SBP and DBP = systolic and diastolic indirect arterial pressure mm Hg S = peak first heart sound amplitude per cent of individual S amplitude at rest WL = work load kilopond meter per minute ΔHR = heart rate increase during exercise beats/min above resting level

stress Measurements of amplitude at given increments of heart rate of 10, 20 etc beats per minute were obtained by linear interpolation Repeat studies in 5 patients with angina pectoris demonstrated a correlation coefficient of 0 67 between measurements of relative S_1 amplitudes during exercise at a heart rate average of 30 beats per minute above the resting level during separate tests 1 week to 1 month apart

Results

Fifteen of the 22 patients developed classic angina pectoris during the exercise test The other 7 patients were limited by precordial discomfort shortness of breath, fatigue or ventricular arrhythmias In all subjects in the control group the findings were normal during the test with respect to ECG heart rate and blood pressure response Mean values for heart rates work loads and blood pressure at rest and during exercise are presented in Table I

Fig 1 and Table I show the relationship between change in S_1 amplitude and change in heart rate for the two normal groups and for patients with coronary disease The changes in normal subjects were unrelated to age as demonstrated by Fig 1 and Table I The difference in S_1 amplitude at peak work load between the two normal groups (Table I) is related to a higher maximal heart rate in the younger group There were no significant S_1 amplitude differences between young and old controls at comparable heart rates, and statistical evaluations of differences between patients and controls were based on the pooled control data The slope of the mean curve for the patients was less steep Amplitude differences were present even at low levels of stress, i e , at a stress level much lower than that required to elicit angina The S_1 amplitude difference between the total patient group and the combined young and middle aged control group was highly significant (t test, $p < 0 01$) at heart rate increments of 10 as well as at rates of 20, 30 and 40 beats per minute above resting levels

Fig 2 presents the individual data on all patients The wide range of variability in the patient group is apparent Five patients who developed angina during the test demonstrated an initial steep increase in S_1 amplitude with increasing heart rate, but developed a negative slope of S_1 amplitude at high work loads This pattern of progression was never seen in the normal group

There was considerable overlap between pa

Peak work load				
HR	*WL*	*SBP*	*DBP*	*S*
166		179	81	1053
6 4		5 1	3 1	120
155		180	86	786
3 9		7 3	7 3	97
< 0 01				
164	[illegible]	180	83	936
	[illegible]	4 2	2 4	[illegible]
129	484	155	85	325
	34	4 9	[illegible]	28
< 0 01	< 0 01	< 0 01		< 0 01

tients and normal subjects at the lower end of the spectrum of S amplitudes as demonstrated by the individual data at normalized heart rate increments of 20 and 40 beats per minute presented in Fig 2 However only 3 of 22 patients exceeded the mean S amplitude increment of the normal group at a heart rate increase of 20 beats per minute and only 1 of 22 patients exceeded this value at a heart rate increase of 40 beats per minute

There was no consistent relationship between the response of S amplitude to exercise and the measurable extent of coronary artery disease in the patient group Patients with one or two major obstructions i e the diameter of the vessel(s) occluded at least 50 per cent were just as likely to show an attenuated increase in S_1 amplitude as were patients with three vessel disease Younger patients tended to develop a greater S amplitude than older patients at any given heart rate No age trend was seen in the control group

Similarly there was no significant correlation between left ventricular end diastolic pressure at rest and the presence or absence of left ventricular dysfunction according to the angiogram and S_1 amplitude response Ten of the 22 patients had evidence of previous myocardial infarction by ECG and by history There was no difference between these patients and the patients without infarction in S amplitude response

The P R interval a known determinant of S_1 amplitude decreased with increasing heart rates to a similar extent among patients and control subjects The mean P R interval at rest was 0 17 second in both patients and normal subjects and the decreases at heart rate increments of 20 and 40 beats per minute also were identical in both groups or 0 02 and 0 04 second respectively

The patients tended to have higher heart rates during exercise at any given external work load and performed less work at any given heart rate The blood pressures did not differ significantly at rest and arterial blood pressure at any given heart rate during exercise was slightly lower in the patient group (Table I) There was no correlation between the absolute level of the heart rate at rest and the magnitude of the increase in S_1 amplitude during exercise in any of the subgroups

Changes in S_1 amplitude in ranges of frequency higher and lower than the 100 Hz used in this study were directionally similar but smaller in magnitude

Discussion

The results indicate that there is a significant group difference between patients with coronary disease and normal control subjects with respect to the response of S_1 to exercise The increase in S_1 amplitude was smaller for any given increase in heart rate in the patient group

Analysis of individual data demonstrated a wide spectrum of S_1 responses in the patient group but two distinctive features emerged (1) Five of the 22 patients (23 per cent) showed a decrease in S_1 amplitude with increasing heart rate at peak exercise levels This pattern was not observed in the normal group (2) An S_1 amplitude response of greater magnitude than the average normal response was observed only in 3 of 22 patients during mild exercise and in a single patient during moderately heavy exercise i e at work loads causing heart rate increases of 20 and 40 beats above the resting level

The phonocardiogram represents a potential and largely unexplored source of information on the mechanical performance of the left ventricle during exercise stress but no previous attempt has been made to evaluate the first heart sound Previous investigators have reported the precipitation of ventricular and/or atrial gallops after exercise[9,10]

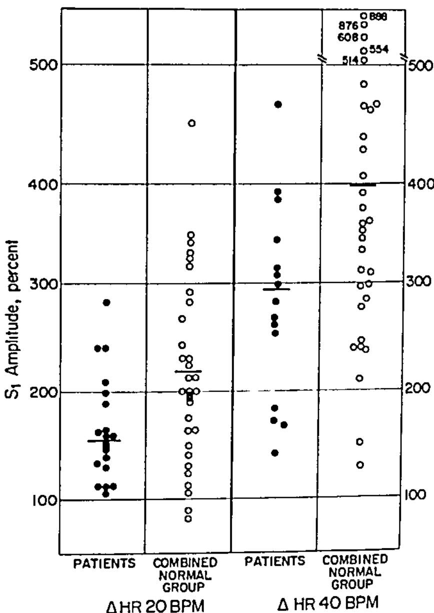


Fig 2 Individual and mean S amplitudes during exercise in normal subjects and in patients with coronary disease S amplitude measured as per cent of the individual amplitude at rest ΔHR equals the increase in heart rate in beats per minute above the resting rate Cross bars denote mean values

There is no clinically applicable method for individual definition of the sound transmission characteristics of the chest Hence, meaningful quantitative interindividual comparisons of am plitudes are not feasible, and the present study was limited to evaluation of exercise induced changes in S_1 amplitude The relative importance of various S_1 determinants is a complex and much debated issue but there is evidence that changes in S_1 amplitude reflect changes in the functional state of the left ventricle [1, 5]

The multiple determinants of S_1 amplitude have recently been reviewed by Luisada and co workers [5] Mechanisms that cause a decreased S_1 amplitude include hypertrophy of the left ven tricular wall, dilatation of the left ventricle, slow rate of rise in left ventricular pressure (dp/dt), and absorption of energy by stretch of elastic (scarred or necrotic) structures in the left ventri cle An increase in S_1 amplitude may be caused by a decrease in compliance a small left ventricle or an increased rate of rise in left ventricular pres sure Variations in left ventricular filling and the rate of rise in pressure generally correlate with variations in S_1 amplitude e g in atrial fibrilla tion and other conditions with varying R R inter val S_1 amplitude and left ventricular dp/dt are frequently decreased in mitral regurgitation No patient in the present study had valvular heart disease or angiographic evidence of mitral regur gitation

Rushmer[11] has related the ' loudness or inten

sity of S_1 to the rate of deceleration of blood during isovolumic contraction and the frequency content to the relative mass (muscle mass and intracavitary blood) and elasticity of the left ventricle The findings in a recent study by Adolph and associates of the characteristics of S particularly the frequency content in patients with myocardial infarction or myocardiopathy and in normal subjects including athletes are consistent with this view

Our results suggest that the difference in S response between patients and controls reflects an abnormal left ventricular response to exercise stress. There was no difference between the groups with respect to P R interval Blood pressures at any given change in heart rate were similar in both groups A variety of direct hemodynamic studies in human subjects and dogs supports the view that (1) acute myocardial ischemia is associated with ventricular dysfunction and (2) the velocity of fiber shortening is an important determinant of S_1 intensity As early as 1932 Orias demonstrated myocardial impairment in dogs after acute coronary artery occlusion Wiggers pointed out that the isovolumic rise in pressure in the left ventricle is slowed during this procedure in the face of an increasing LVEDP

Cohen and associates demonstrated a decline in mean systolic ejection rate during exercise induced angina pectoris The reduced ejection rate was associated with a subnormal cardiac output due to a decreased stroke volume during angina Numerous recent hemodynamic studies (reviewed by Ross) have demonstrated transient left ventricular dysfunction during exercise induced angina pectoris

Sakamoto and co workers have demonstrated that there is a linear correlation between the amplitude of S and left ventricular dp/dt under a variety of experimental conditions These observations have been verified in our laboratory (unpublished results) after the administration of isoproterenol and propranolol in a series of 5 dogs A catheter tip manometer was used for recording left ventricular pressure and derivation of left ventricular dp/dt Heart rate and P R interval were kept constant by means of combined atrial and ventricular pacing Further clinical support for a relationship between contractile state and S amplitude was obtained in 4 patients with angina pectoris who were studied according to the protocol used in the present study before and after relatively large oral doses of propranolol maintained for at least 1 week (average of 160 mg per day divided into 4 doses) The average increase in S_1 at a heart rate of 40 beats per minute was 197 per cent in the control study compared to 96 per cent when the patients were on propranolol (unpublished data)

The presence of an overlap between patients and control subjects and the apparent lack of correlation between S_1 response and resting hemodynamic and angiographic indices of myocardial function are hardly surprising In the present study measurements were normalized individually with respect to S amplitude at rest Thus it is likely that changes in S amplitude reflect changes in contractile state in response to exercise stress which may not be closely related to ventricular performance characteristics at rest

It is conceivable that differences with respect to autonomic nervous system regulation of the cardiovascular response to exercise contributed to the difference in S_1 response between patients and control subjects However the fact that S_1 amplitudes were related to heart rate rather than to severity of exercise measured as work load or oxygen uptake should minimize any group differences in terms of the level of sympathetic stimulation

Measurements of S_1 amplitude at rest and during exercise are easily obtained The results of the present study suggest that clinically useful information can be derived from analysis of the response of S_1 amplitude to exercise stress

Summary

The response of S_1 amplitude to exercise stress was investigated in patients with coronary heart disease. Phonocardiograms were recorded at rest and during a multistage bicycle ergometer exercise test in a group of 22 patients with angina pectoris and documented coronary disease and in a normal control group comprised of 32 men A symmetrical bandpass filter with 100 Hz center frequency and a 12 db per octave slope was used

Mean S amplitude increased approximately linearly with heart rate from rest to maximal exercise through several levels of submaximal

effort in both control groups An increase in heart rate of 40 beats above resting levels resulted in a mean increase in S_1 amplitude of 281 per cent in the control group There was a significantly smaller ($p < 0.01$) mean increase in the patient group 195 per cent In 5 patients the S_1 amplitude during exercise at the load precipitating angina was lower than at the highest load that could be tolerated without pain

S_1 amplitude is easily measured and may provide a clinically useful method for evaluation of left ventricular function and documentation of an abnormal left ventricular response to exercise stress

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Experimental and laboratory reports

Body surface isopotential mapping in Wolff-Parkinson White syndrome Noninvasive method to determine the localization of the accessory atrioventricular pathway

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Several hypotheses have been proposed for the elucidation of the genetic mechanism of the electrocardiographic (ECG) pattern of the Wolff Parkinson White (WPW) syndrome[7] However the accessory atrioventricular pathway theory has come to be the more influential concept to explain its mechanism because of surgical reversion of the paroxysmal tachycardia often associated with the WPW syndrome[6]

For localizing the accessory pathway pattern classifications[8] by conventional ECG or vectorcardiogram have been utilized Recently it was reported that localizing early ventricular excitation was improved by a direct lead ECG from the epicardial surface[5] However this method is not noninvasive and there are limitations on checking the relevant examining areas during the limited period of surgical operation with possible loss of accuracy To overcome this problem clinical investigation of body surface isopotential mapping has been recommended as an alternative noninvasive technique

There are few reports concerning clinical investigation of the WPW syndrome by body surface isopotential mapping[5] We examined 22 cases of WPW syndrome by body surface isopotential mapping and this report mainly deals with the analysis of results correlation of the pattern of mapping and the classification of conventional ECG patterns of this disease entity

Method

Localizations of lead points (Fig 1) For the construction of body surface isopotential maps 85 lead points were distributed over the chest wall and the upper abdominal surface with points concentrated on the anterior chest wall and less on the back (Fig 1) Paste filled disposable electrodes of 1 1 cm diameter were used

Data processing (Fig 2) A unipolar lead ECG recording was made at each of 85 lead points with Wilson s central terminal as the reference point During the expiratory phase ECG data from any two lead points were fed into analog to digital converters simultaneously with the Lead II ECG These data were processed by a mini digital

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Fig 1 Black circles shown on the anterior (top) and posterior (bottom) thoracic surface represent the 85 unipolar lead points for the unipolar lead ECG s

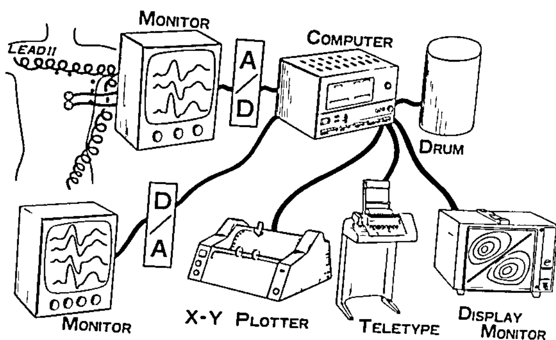


Fig 2 Schematic representation of the system and procedure used for data acquisition and processing Two unipolar lead ECG s were fed into the computer along with Lead II ECG used as the time reference via a monitor scope and A/D converter

computer (Nihon Denshi Co Model JEC 5 magnetic core memory capacity 4 kilo words of 16 bits) after analog to digital conversion Sampling rate was about 2 600 per second for each lead Time synchronization was carried out with the Lead II ECG used as the time synchronization ECG The zero level was determined by averaging 32 points in a flat portion of T P interval In order to be assured of high quality for these two factors after synchronization the data were called back via digital to analog conversion and reviewed on the monitorscope If found acceptable, the data were then sent to the drum and stored there The input and processing of these data were repeated 43 times to obtain all data from 85 lead points After storage of all data the body surface isopotential maps were constructed by means of teletype X Y plotter, or CRT display

Clinical material (Table I) The clinical material consisted of 22 patients with WPW syndrome without any other overt cardiovascular complication, 11 males and 11 females Age distribution ranged from 10 to 63 years with an average of 34 years

The P R interval was noted to be 0 060 sec minimum and 0 120 sec maximum and all cases

Table I ECG findings in 22 patients with WPW syndrome

Case no	*Sex*	*Age*	*Paroxysmal tachycardia*	*Form of V*	*ECG class*	*P R (sec)*	*QRS duration (sec)*	*P-J (sec)*	*Type of map*	*Appearance of saddle" (sec)*
26	M	63	+	rs(r=s)	AB	0 1"0	0 150	0.2"0	I(a)	0 0"2
"7	F	10	+	Rs	A	0 100	0 094	0 194	I(a)	0 0[illegible]9
3"	M	48	+	Rs	A	0 100	0 140	0 240	I(a)	0 104
82	F	34	+	Rs	A	0 100	0 099	0 199	I(a)	0 072
					Average	0 10[illegible]	0 121	0 225		0 077
15	M	28	+	rSr's	B	0 120	0 108	0 "28	I(b)	0 041
[illegible]8	F	19	+	rs(r=s)	AB	0 1"0	0 12'	0.22"	I(b)	0 054
20	F	"0	−	qrs	B	0 120	0 099	0 219	I(b)	0 0[illegible]0
45	M	38	−	rS	B	0 100	0 104	0 204	I(b)	0 041
					Average	0 115	0 108	0 218		0 047
					Average	0 110	0 115	0 2"2		
23	F	56	+	rS	B	0 060	0 158	0 "18	II	
[illegible]8	F	20	+	rS	B	0 080	0 162	0.242	II	
38	M	58	+	rS	B	0 080	0 1[illegible]3	0 233	II	
43	M	3	−	rS	B	0 080	0 180	0.260	II	
68	F	26	+	rS	B	0 100	0 1[illegible]5	0.23[illegible]	II	
8[illegible]	F	45	+	rS	B	0 080	0 172	0.2[illegible]2	II	
8[illegible]	M	48	+	rS	B	0 080	0 162	0.24"	II	
					Average	0 080	0 160	0.240		
21	F	36	+	QS	C	0 100	0 153	0.253	III	
24	M	16	−	QS	C	0 100	0 135	0.235	III	
42	F	17	−	QS	C	0 100	0 144	0 244	III	
					Average	0 100	0 144	0 244		
3"	F	29	−	QS	C	0 100	0 144	0 244	Undetermined	
33	M	33	+	rsr's	AB	0 100	0 123	0.233	Undetermined	
39	M	42	−	Rs	A	0 080	0 1"6	0 206	Undetermined	
46	M	42	+	rS	B	0 080	0 143	0.222	Undetermined	

showed shortening of the P R interval with an average duration of 0 098 sec All cases showed prolongation of QRS interval with a minimum of 0 094 sec a maximum of 0 180 sec and an average of 0 132 sec The P J interval was 0 193 sec in minimum 0 270 sec maximum average 0.230 sec

According to the ordinary classification of ECG patterns proposed by Rosenbaum and Ueda and their co workers there were four cases with Type A 11 cases with Type B four cases with Type C and three cases unclassified (i e rather difficult to classify into A or B type because the amplitude ratio R/S was nearly 1 in Lead V hereafter this type is labeled Type AB)

ECG data were recorded at a time when there was no attack of paroxysmal tachycardia in all 22 patients

For the construction of the normal pattern body surface isopotential map nine normal adults (age distribution 23 to 45 years) volunteered as a control group

Results

For illu trating the body surface isopotential map (hereafter abbreviated as map) the map was cut and separated along the right midaxillary line on the thoracic surface and was fanned and spread open (Figs 3 5 7 9 and 11)

The black area illustrates the positive zone and the white area the negative zone fine solid lines in each zone illustrate an isopotential line for each 0 4 mV and the interrupted line illustrates the potentials of Wilson s central terminal which may be called the zero line The QRS complex of the Lead V ECG is shown at the right upper corner of each figure expressing the serial maps (Figs 3 5 7 9 and 11)

In the present investigation the maps recorded from 22 patients with WPW syndrome were

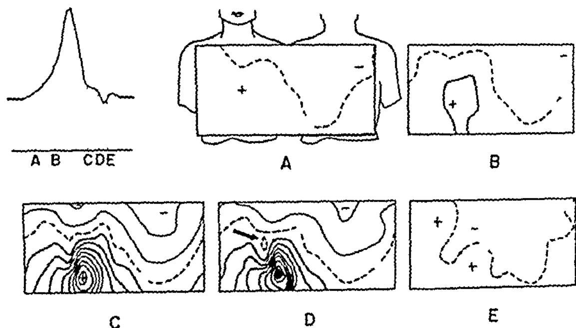


Fig 3 A representative time course of the Type Ia map pattern of WPW syndrome The letter underlying each map shows the instant when the map pattern was obtained The instants were indicated under the QRS complex of Lead V_1 ECG shown in the left upper inset *A* 18 *B* 45 *C* 99 *D* 104 and *E* 130 msec after the onset of QRS complex respectively Note that the negative zone covered the back throughout the entire period of the ventricular activation and that a small isolated negative zone indicated by the arrow was observable in the map marked *D*

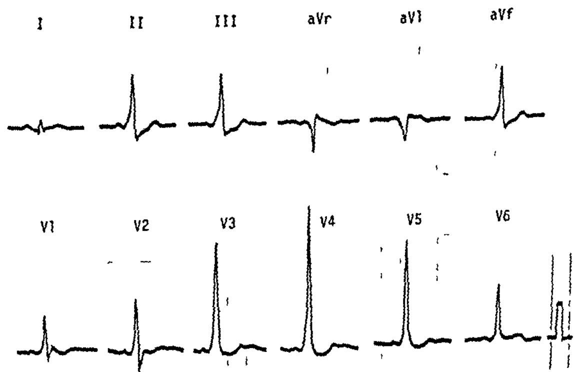


Fig 4 The standard 12 lead ECG s obtained from the patient represented in Fig 3

classified into three types (Type I, Type II, and Type III) by analyzing characteristic patterns of potential distribution at the early stage of ventricular excitation (namely the stage of delta wave appearance) the middle stage of ventricular excitation, and of the late stage It was possible to classify them into three categories except some cases which could not be classified into any of three types and this group was termed unclassified type

Body surface isopotential map of Type I Eight out of 22 cases showed this pattern There were two subtypes Ia (four cases) and Ib (four cases) from the pattern of the late stage of ventricular

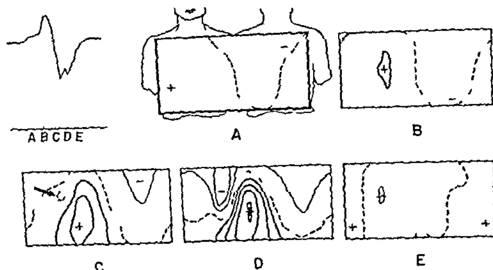


Fig 5 A representative time course of Type Ib map pattern of WPW syndrome *A* 18 *B* 45 *C* 54 *D* 77 and *E* 104 msec after the onset of QRS complex respectively Note that a small isolated negative zone indicated by the arrow in the map marked *D* appeared earlier compared with that in Type Ia map See text for explanations

excitation as may be seen in Figs 3 and 5 At 18 msec after the initiation of ventricular excitation which corresponded to the time when the delta wave appeared in the conventional ECG the positive zone covered the anterior chest wall whereas the negative zone covered the back as may be seen in Fig 3 *A* The potential map recorded at 45 msec which was the time when the delta wave passed over resembled the map recorded at 18 msec in its distribution as may be seen in Fig 3 *B* At 99 msec difference in magnitude between the points of the maximum and of the minimum became largest the maximum was located at the lower part of the left sternal border and the two minima appeared the one at the upper margin of the sternum and the other at upper part of the back The positive zone occupied the lower two thirds of the anterior chest wall whereas the negative zone occupied almost the entire back and the upper third of the anterior chest wall as may be seen in Fig 3 *C*

A small negative zone appeared over the sternum at the fifth intercostal space within the positive zone at the anterior chest surface as indicated by the arrow in Fig 3 *D* at 104 msec The location of this small negative zone may correspond to the location of the saddle * observed in normal persons early in ventricular excitation The small negative zone further expanded and fused into the negative zone covering the upper anterior chest wall At 130 msec the positive zone covered the right anterior chest surface and the lower half of the left anterior chest surface whereas the negative zone covered the back and the upper half of the left anterior chest surface One of the two maxima was located at the lower part of the left anterior chest surface and the other at the upper part of the right anterior chest surface each by each (Fig 3 *E*) Characteristic of the Type Ia map was that the negative zone covered the back throughout the entire period of ventricular excitation The conventional 12 lead ECGs recorded from the patient showing the Type Ia pattern are illustrated in Fig 4

A representative case with a Type Ib map is shown in Fig 5 In map patterns recorded at the times of 18 and 45 msec after the initiation of ventricular excitation (Fig 5 A and B) the pattern resembled the Type Ia map as shown in Fig 3 *A* and *B* The negative zone covered the back and the upper right anterior chest surface at 54 msec An isolated negative zone appeared on the sternum at the fourth intercostal space within the positive zone covering the entire anterior chest surface as indicated by the arrow in Fig 5 C This special pattern in which the negative zone appeared within the area of the positive zone was observed at 104 msec in the case with Type Ia The negative zone observed at the upper right anterior chest surface and small negative zone observed on the sternum at the fourth intercostal space fused with each other and this negative zone expanded to the right anterior

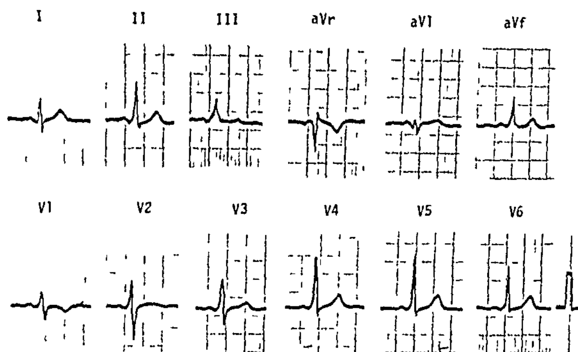


Fig 6 The standard 12 lead ECG s obtained from the patient represented in Fig 5

chest surface as shown in Fig 5 *D* At 101 msec the positive zone occupied a region extending from the right midaxillary line to just anterior of the right anterior axillary line and the right back, whereas the negative zone occupied remainder of the entire anterior chest as well as the left back Two maxima appeared one at the lower part of the right anterolateral chest surface and the other at the lower part of the right back A minimum was located on the sternum at the fifth intercostal space as seen in Fig 5, *E* The conventional 12 lead ECG s recorded from the same patient showing this map pattern are illustrated in Fig 6

Cases showing the Type Ia map pattern included three cases with Type A ECG classification and one case with Type AB The P R interval averaged 0 105 sec and the QRS interval 0 121 sec Attacks of paroxysmal tachycardia were assured in all cases from the clinical history of the patients As mentioned above the time when the negative zone appeared within the area of the positive zone averaged 0 077 sec after the onset of QRS complex (Table I)

Cases showing the Type Ib map pattern included three with Type B ECG and one with Type AB The P R interval averaged 0 115 sec and the QRS interval 0 108 sec Paroxysmal tachycardia was observed in two cases in this group The negative zone appeared within the area of the positive zone at an average of 0 047 sec (Table I)

There were statistically significant differences in P R intervals and also QRS intervals between groups with Type Ia and Type Ib On analyzing the time course of the map patterns the stage when the negative zone appeared within the positive zone was later in the time sequence of the excitation process in Type Ia as compared with Type Ib

Body surface isopotential map of Type II (Fig 7) Seven out of 22 cases displayed the Type II map pattern of which a representative pattern is illustrated in Fig 7 At 18 msec after the initiation of ventricular excitation namely at the stage when the delta wave appeared on the conventional ECG, the zero potential line ran at the right sternal border and at the back longitudinally, and the positive zone occupied the entire left anterior chest surface and the left half of the back whereas the negative zone occupied the right anterior chest surface and the right back The maximum was located in the vicinity of the sternum at the fourth intercostal space and the minimum was located at the lower part of the right anterior chest surface as shown in Fig 7, *A* At 42 msec the zero potential line at the anterior chest surface shifted leftward to some extent There was no remarkable change in location of the zero potential line seen at the back, as shown in Fig 7, *B* At 78 msec the zero potential line at the anterior chest surface shifted farther to the left and the maximum and minimum also shifted leftward along the shift of the zero potential line

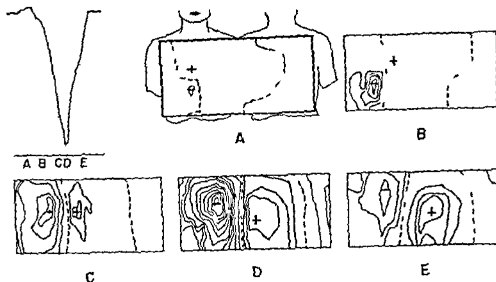


Fig 7 A representative time course of Type II map pattern of WPW syndrome *A* 18 *B* 42 C 78 D 108 and *E* 150 msec after the onset of QRS complex respectively Note that the two longitudinal zero lines shifted toward the left almost in parallel along with the progress of the ventricular activation See text for detailed explanations

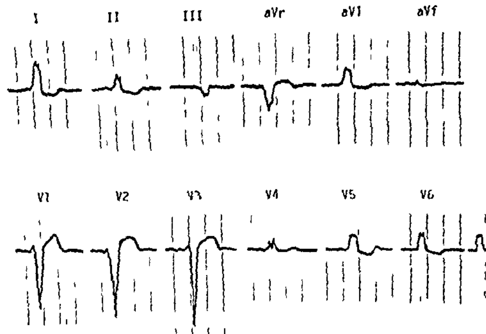


Fig 8 The standard 12 lead ECG s obtained from the patient represented in Fig 7

However the zero potential line at the back hardly shifted as shown in Fig 7 *C* At 108 msec the potential difference between the maximum and minimum became largest the zero potential line ran over the left midclavicular line longitudinally and there was no remarkable change in location of the zero potential line at the back (Fig 7 *D*) At 150 msec the running direction of the zero potential line was almost the same as that at 108 msec as shown in Fig 7 *E* The characteristic features of the Type II map pattern were that the zero potential lines ran longitudinally on the anterior chest surface and the back throughout the entire course of the ventricular excitation

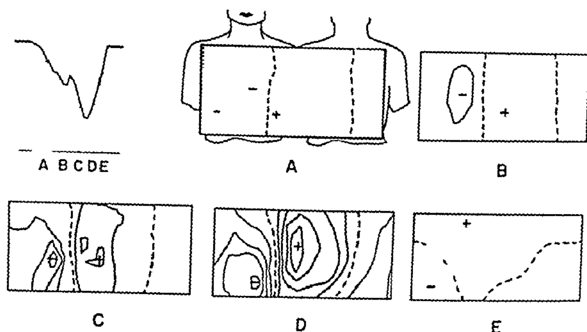


Fig 9 A representative time course of Type III map pattern of WPW syndrome A 18 B 45 C 72 D 99 and E 135 msec after the onset of QRS complex respectively Note that the negative zone seen at the anterior chest surface at 18 msec expanded more leftward compared with that in Type II map of the same instant and that a positive zone appeared on the anterior upper chest surface at 135 msec See text for detailed explanations

process and the zero potential line at the anterior chest surface showed a parallel shift leftward as the ventricular excitation process proceeded There was no remarkable change in the shift of the zero potential line over the back throughout the entire process of ventricular excitation A representative pattern of the conventional 12 lead ECG s recorded from the patient showing the Type II map pattern, is illustrated in Fig 8 and this ECG pattern was noted to be of Type B in all cases

The P R interval averaged 0 08 sec and was markedly shortened in all cases the QRS interval averaged 0 163 sec and always was markedly prolonged Paroxysmal tachycardia was observed six out of seven cases (Table I)

Body surface isopotential map of Type III (Fig 9) Three out of 22 cases showed the Type III map pattern, a representative pattern is illus trated in Fig 9 At 18 msec after the initiation of ventricular excitation the zero potential line ran at the left sternal border and at the midline of the back longitudinally The maximum was located at the lower part of the right anterior chest surface Two minima were located one on the sternum at the fifth intercostal space and the other at the lower part of the right anterior chest surface as shown in Fig 9 *A* At 45 msec the zero potential lines were at almost the same locations as shown in Fig 9 *B* At 72 msec the maximum shifted to the left midclavicular line at the fourth intercostal space and the minimum shifted to the lower part of the sternum whereas the location of the zero potential line was almost the same as that at 45 msec as shown in Fig 9 *C* At 99 msec the location of the maximum shifted somewhat leftward and the minimum shifted downward to some extent and the potential difference became largest in magnitude at that time but the location of the zero potential line was almost the same as that at 45 msec (Fig 9 *D*) At 135 msec the zero potential lines located at the anterior chest surface and at the back changed their direction rather transversely These two lines seemed to be fused at the lower part of the left anterior chest surface with the upper part (i e above the zero potential line) observed to be the positive zone whereas the lower part was the negative zone with the maximum located at the upper part of the thorax and the minimum at the lower part of the right anterior chest surface as shown in Fig 9 *E* As mentioned above the locations of the zero potential lines in Type III cases resembled those of Type II from the onset of the ventricular excita tion process up to 72 msec However the location of the zero potential line at the early stage of ventricular excitation was located rather right ward in Type II cases and rather leftward in Type III cases There was no remarkable difference as to the location of the minimum in both Type II and Type III but the magnitude of the potential

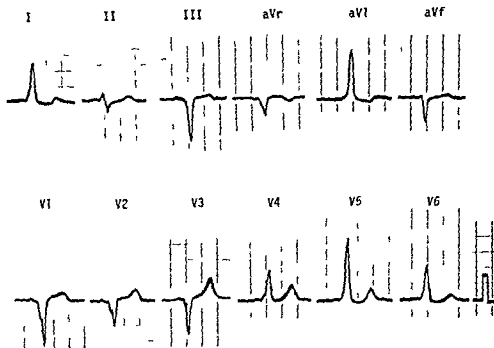


Fig 10 The standard 12 lead ECG s obtained from the patient represented in Fig. 9

of the minimum in Type II was smaller than in Type III The location of the maximum at the upper margin of the sternum observed in the late stage of ventricular excitation resembled that observed at the anterior chest surface on the map pattern of normal persons The conventional 12 lead ECG s recorded from the same patient showing the Type III map pattern are illustrated in Fig 10 All three cases showing the Type III map pattern belonged to Type C of the ordinary ECG pattern classification proposed by Ueda and associates

The P R interval was short in all cases averaging 0 10 sec and the QRS interval was markedly prolonged averaging 0 144 sec Paroxysmal tachycardia was observed in one out of three cases (Table I)

Undetermined or unclassified type Four out of 22 cases belonged to the unclassified type because these cases could not be classified into any of the three types mentioned above For example as illustrated in Fig 11 the positive zone was located at the upper part of the anterior chest surface and the upper part of the back whereas the negative zone was located at the lower part of the right anterior chest surface and at the lower part of the right back, with the minimum at the lower part of the right back during early stage of the ventricular excitation process that is the stage in which the delta wave appeared on the conventional 12 lead ECG s At 41 msec after the initiation of ventricular excitation the area of negative potential appeared within the area of the positive zone as shown in Fig 11 *B* At 81 msec the zero potential line ran transversely on the anterior chest surface and back and the positive zone covered the upper half of the anterior chest surface and the upper half of the back whereas the negative zone covered the lower half The maximum was located at the upper left sternal border and the minimum on the lower part of the right anterior chest surface and at the sternum at the fifth intercostal space as shown in Fig 11 *E* The conventional 12 lead ECG s recorded from the same patient are illustrated in Fig 12 Two out of four cases showed such a map pattern One of the other two cases showed the Type III pattern during the early stage of ventricular excitation and later showed the Type II pattern during the late state of excitation whereas the other case showed the opposite pattern

Discussion

There are several hypotheses to explain the genetic mechanism of the WPW syndrome [4] Recently several successful results have been

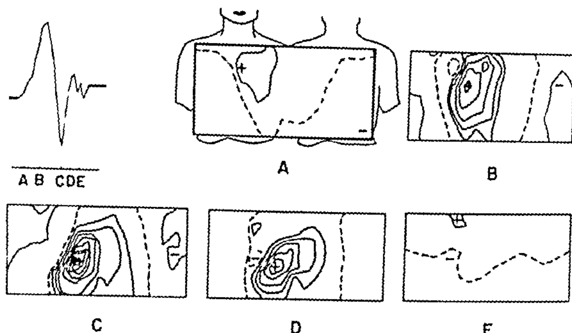


Fig 11 An example of isopotential maps which did not belong to any of the three types of map pattern *A* 18 *B* 41 *C* 59 *D* 68 and *E* 81 msec after the onset of QRS complex See text for detailed explanations

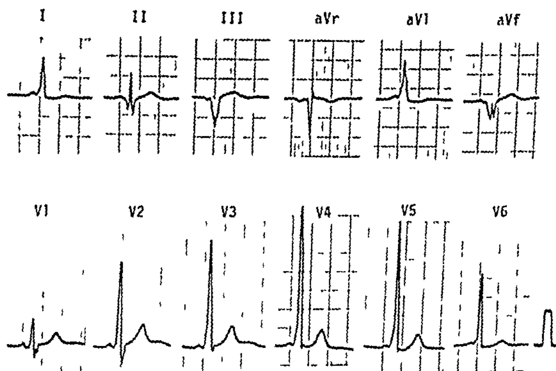


Fig 12 The standard 12 lead ECG s obtained from the patient represented in Fig 11

reported for surgical treatment in cases of WPW syndrome associated with attacks of paroxysmal tachycardia, from the viewpoint of an accessory atrioventricular pathway theory[5, 8, 10] The conventional 12 lead ECG's[4] and vectorcardiogram[9] have been used heretofore as diagnostic approaches to determine the localization of an accessory atrioventricular pathway but the results obtained by these diagnostic approaches in some instances disagree with the results obtained from the analysis of the ventricular excitation on the direct lead epicardial surface ECG[17] However there are some limitations and problems involving recording of the direct lead electrogram from the epicardial surface within the short period of time before operation and also that this recording can be performed only on the anterior surface of the heart Therefore, it is to be hoped that a noninvasive method to determine the localization of any accessory atrioventricular

pathway could be carried out as the diagnostic approach

Recently there are some interesting reports of clinical[6] [27] and experimental [26] investigations of the body surface isopotential map of the cardiac potential According to these reports the maps have more diagnostic informations about the ventricular excitation process than the conventional ECG or vectorcardiogram It is thought that the direction of the resultant vector of cardiac electromotive force can be inferred from analyzing the distribution of the positive and negative zones and the location of the maximum and minimum and that the map thus displays even the ventricular excitation process [5] Nevertheless there is no report of the WPW syndrome being investigated from the view point of the body surface isopotential map with the results correlated with the pattern of the conventional ECG Therefore these investigations were carried out in the present study

Fewer recording electrodes were used to construct the map in the present study compared with those used by other investigators However the normal maps obtained from nine Japanese male adults agreed with the map reported by Taccardi and associates [2] and in the pilot study the maps were recorded twice from the same normal individual one month apart and it was verified that there was no difference between two maps Thus the authors were convinced that the technique used in the present investigation was satisfactory

At the stage when the delta wave appears in the conventional ECG the Type Ia map displays a positive zone occupying the anterior chest surface and a negative zone occupying the back Therefore it appears that the excitation wave front proceeds from the posterior toward the anterior part of the heart (Fig 3 *A*)

A small negative zone appears within the area of the positive zone at 104 msec and this pattern closely resembles the pattern of the so called saddle in the normal map proposed by Taccardi Therefore it is inferred that the excitation wave front reaches the epicardial surface of the right ventricle at this stage (Fig 3 *D*) In the late stage of ventricular excitation at 130 msec the positive zone occupies the right anterior and the left anteroinferior surfaces whereas the negative zone occupies the back and the left anterior superior surface the positive zone at the right superior anterior area is considered to be caused by the excitation of the area of the A V sulcus region of the right ventricle and of the pulmonary artery conus In the map of the normal person the positive zone can be seen at the right antero superior area and on the back whereas the negative occupies the back in the Type Ia map at the late stage of ventricular excitation This pattern indicates that the posterior basal aspect of the left and the right ventricles which usually is activated at the later stage during normal ventricular excitation has already completed excitation in cases of Type Ia (Fig 3 *E*)

As mentioned above in the Type Ia map the negative zone covers the back throughout the entire stage of ventricular excitation and the pattern resembling the saddle appears at a rather late stage so that the location of early excitation can be presumed to be at the postero basal aspect of the left ventricle

In the Type Ib map the excitation wave front is directed from the posterior aspect of the heart toward the anterior aspect at the stage when the delta wave appears and this pattern closely resembles the Type Ia map pattern (Fig 5 *A* and *B*) The Type Ib map pattern closely resembles that of Type Ia in potential distribution after that stage but the negative zone appears within the area of the positive zone already at the stage of 54 msec which is similar to the phenomenon of the saddle This negative zone which appears earlier in Type Ib than in Type Ia (Fig 5 *C*) may be considered to represent the time when the excitation wave front reaches the epicardial surface of the right ventricle Next at 104 msec in the later stage of ventricular excitation the positive zone covers the right lateral chest surface and the back and the maximum which usually does not appear in the case of normal excitation appears at the lower part of the right back This finding may support the evidence that there is an exciting region at the posterobasal aspect of the right ventricle (Fig 5 *E*)

From the above mentioned findings it appears that (1) part of the early excitation may be located at the posterobasal aspect of the left ventricle in Type Ib as well as Type Ia (2) the phenomenon similar to saddle appears earlier in Type Ib than in Type Ia and (3) the QRS duration in Type Ib is shorter than that in Type Ia Thus the location of early ventricular excitation is at the posterobasal part of the left

ventricle in Type Ib as well as Type Ia, and it may be considered that there is a time difference in fusion with normal sinus rhythm between Type Ia and Type Ib

In the cases showing the Type II map pattern the negative zone occupies the right anterior chest surface and the right back at the stage when the delta wave appears on the conventional ECG and the minimum with much greater potential, which can not be seen in the case of the normal map, is located at the lower part of the right anterior chest surface From these findings it is thought that the excitation wave front proceeds from the side of the right ventricle toward the left ventricle

At 108 msec which can be considered to be the middle stage of ventricular excitation the cardiac electromotive force is considered to be directed from right superior anterior to left inferior posterior judged from the locations of the maximum and minimum as it resembles the normal pattern (Fig 7 D) It was observed that there was no positive zone occupying the upper part of the right anterior chest surface and the right back (which was usually observed in the case of normal excitation at the late stage of excitation), and it is speculated that excitation at the part of pulmonary conus and/or A V sulcus region at the posterobasal part of the right ventricle, which usually is excited in the latest stage of normal excitation could have been already completed The positive zone remains on the left lateral chest surface and the left back, and this may indicate a time lag of excitation of the ventricular portion (Fig 7 E) From the above observations it appears that the location of early ventricular excitation is at the basal part of the right ventricle and the vicinity of the pulmonary conus

The Type III map pattern resembles that of Type II except the early and late stages of ventricular excitation In the early stage the zero line seen in the anterior chest surface of the Type III map (Fig 9 A) situated more leftward than that of the Type II map (Fig 7, A) and the negative zone in the Type III map occupied more than the right half of the chest surface that is the region extending from the vertebral line as far as the left parasternal line Furthermore the two minima were observed in the Type III map (Fig 9 A), the one is located rather to the right and inferior compared with the minimum seen in the Type II map of the corresponding stage (Fig 7, A) and the other is located at the site where the 'saddle' appears in normal map pattern It is known that 'saddle' implies the arrival of ventricular excitation at the right ventricular epicardial surface and therefore such evidence that the anterior chest surface up to the left sternal border was covered by the negative zone at the early stage implies that the anterior surface of the right ventricle is excited in the early stage Hence it appears that part of the early excitation can be located at the vicinity of the ventricular septum within the posterior aspect of the right ventricle It may be thought that the excitation wave front proceeds from the inferior aspect of the right ventricle to the posterior aspect of the left ventricle at the peak of ventricular excitation In the Type III map pattern (Fig 9 E) during the late stage of excitation, differing from the Type II map the positive zone occupies almost the entire anterior chest surface except an inferior wedge of the anterolateral portion of the right chest, as shown in Fig 9 E Thus the excitation of the pulmonary conus region and the A V sulcus region may be late as is that of normal excitation

Three out of four cases with Type A by ECG classification showed the Type Ia map pattern (Table I) There were several reports that the location of early ventricular excitation was on the left ventricular side in cases with ECG classification Type A, and this finding agrees with and supports our finding that the location of early excitation is at the posterobasal aspect of the left ventricle Seven out of 11 cases with Type B by ECG classification showed the Type II map pattern, three cases with Type B showed Type Ib, and the remaining one case with Type B showed the unclassified map pattern Rosenbaum and associates stated that part of the early excitation is located at the right ventricular site in cases with Type B and the finding of the ventricular excitation process,[5, 6, 11] which was obtained by the direct lead electrogram from the epicardial surface during surgical operation also supported his proposal However Ueda and his associates[9] confirmed that early excitation is located at the posterobasal part of the left ventricle in some instances with Type B by using an esophageal lead By analyzing the vectorcardiographic pattern, it was reported[10] that the Type B ECG pattern can appear if the degree of fusion is in

lesser degree although early excitation is considered to take place at the posterobasal aspect of the left ventricle This evidence was also supported by the experimental finding[8, 29] that the Type A or B ECG pattern can be produced by changing the degree of fusion although the location of the early excitation is the same Furthermore there was the report[17] that early excitation was located at the posterobasal aspect of the left ventricle in cases showing Type B by checking the finding obtained from the direct lead ECG from the epicardial surface

Also in the present investigation Type Ib map pattern in which the early excitation occurs at the posterobasal aspect of the left ventricle was found in the cases with ECG pattern of Type B

Therefore it may be dangerous to judge that part of the early excitation is located in the right ventricle in all cases showing ECG pattern Type B Three cases out of four with ECG pattern Type C showed the Type III map pattern and the remaining one case belonged to the unclassified type Ueda and his associates[1, 29] reported that part of the early excitation was located at the basal aspect of the right ventricle in cases showing ECG pattern Type C and furthermore they verified experimentally that this part was located at the posterobasal aspect of the right ventricle[2] Their results agreed with our finding that part of early excitation was located in the vicinity of the ventricular septum at the posterior aspect of the right ventricle in cases showing the Type III map pattern Cole and his associates[5] also reported that the accessory atrioventricular pathway was located at the ventricular septum in the vicinity of the A V node in cases showing a QS pattern in chest Lead V and Lindsay and his associates also stated that part of early excitation located in the vicinity of the ventricular septum at the posterobasal aspect of the right ventricle in similar cases

Summary

The body surface isopotential maps of 22 patients with WPW syndrome were obtained from the 85 unipolar lead ECG s using the on line minicomputer system newly devised by the author s group

The map patterns were classified into three types—I II and III (Type I eight Type II seven Type III three and unclassified four cases) In Type I the back surface displayed the negative potential throughout the entire ventricular activation and at the terminal stage the lower precordial area displayed the positive potential and the upper precordial area the negative one Type II was characterized by two longitudinal lines one staying at its place on the back and the other moving right to left on the precordial area following the process of ventricular activation In Type III the right precordial area displayed negative potential in the early stage and in the terminal stage the upper part of the right side of chest surface displayed positive potential and the lower part negative potential

It was surmised from these patterns that the pre excited area was located at the posterior region of the ventricles in Type I at the right ventricle in Type II and the right ventricular base near the posterior margin of the ventricular septum in Type III

Type A patients in the conventional ECG classification fell under Type I Type C patients under Type III Type B patients under either Type I or Type II

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The effect of upright tilt on the volume of the failing human left ventricle

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Although the hemodynamic alterations induced by change from supine to head up tilted or erect position have been extensively studied in both normal subjects and patients with heart dis ease information concerning the quantitative effect of postural changes on the volume of the left ventricular cavity is incomplete Thus several investigators have reported that transi tion from supine to tilted or erect posture has resulted in a decrease in the volume of the heart as determined by radiographic[1] [5] or isotopic methods which however detect the combined volume of the heart rather than that of the left ventricular cavity per se Studies have been conducted by Rushmer on the effect of posture on the canine left ventricular diameter but have not been extended to human beings Rapaport and associates have studied the effect of posture on the volume of the normal and the failing right ventricle and similar studies concerning the left ventricle have been conducted in 6 normal sub jects but not in patients with heart failure

It has been demonstrated that the internal dimension of the human left ventricle can be mea sured throughout the cardiac cycle by echocar diography and that this dimension provides useful information concerning the volume of the left ventricle in most cases[2] [25] Therefore the present study was designed to establish and quan titate the effect of upright tilt on the volume of the failing left ventricle as determined by echo cardiography

Methods

The study population consisted of 36 subjects (24 males) whose ages ranged from 8 to 58 (average 33 4) years They were divided into 3 groups *Group I* consisted of 18 subjects mostly volunteers with no evidence of heart disease as determined by history physical examination and electrocardiogram (Table I) *Group II* (Table II Nos 1 6) included 6 patients with compensated left ventricular (LV) volume overloading due to either aortic regurgitation or mitral regurgitation or both In addition mild mitral stenosis was pre ent in 2 patients No patient in this group had previously undergone cardiac catheterization All patients were in Class I or II according to the functional classification criteria of the New York Heart Association (N Y H A) * The symptoms and physical findings are listed in Table II *Group III* (Table II Nos 7 18) included 12 patients with congestive heart failure due to congestive cardio myopathy (7 patients) chronic hypertensive car diovascular disease (1 patient) both (2 patients) or congestive cardiomyopathy combined with mild coronary artery disease (2 patients) All were in Class III or IV according to the aforemen tioned N Y H A criteria The diagnosis of conges tive heart failure was established from the pres ence of at least seven of the ten clinical or lab oratory criteria shown in Table II With regard to these criteria the jugular venous pressure was deemed to be abnormal if higher than 3 cm above

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Table II Clinical and other data in Groups II and III

Patient No	High JVP	S gallop	Râles	Edema	Effort dyspnea	PND or orthopnea	Pulsus alternans	PEP/ET > 0 4?	EF < 0.5	CT > 0 5	NYHA class	Diagnosis
Group II (compensated left ventricular volume overloading)												
1	–	+	–	–	–	–	–	–	–	+	I	MR
2	–	–	–	–	+	–	–	–	–	+	II	AR
3	–	–	–	+	–	–	–	(LBBB)	–	+	I	AR
4	–	–	–	–	+	–	–	–	–	+	II	AR + MR + MS
5	–	+	–	–	–	–	–	–	–	+	I	MR
6	–	+	–	–	+	–	–	Unobt	–	+	II	AR + MR + MS
Group III (congestive heart failure)												
7	+	+	–	+	+	–	–	+	+	+	III	CMP
8	–	+	+	+	+	+	–	+	+	+	III	CMP + CAD
9	+	+	+	+	+	+	–	Unobt	+	+	IV	CMP
10	+	+	+	+	+	+	–	(LBBB)	+	+	IV	CMP
11	–	–	–	+	+	+	+	+	+	+	III	CMP
12	–	+	+	–	+	+	–	+	+	+	III	HPT
13	+	+	+	–	+	–	–	+	+	+	III	CMP + HPT
14	+	+	–	+	+	–	–	+	+	+	III	CMP
15	+	–	+	–	+	+	+	+	+	+	III	CMP
16	–	+	+	–	+	+	–	(LBBB)	+	+	IV	CMP + CAD
1	+	+	–	+	+	+	–	+	+	+	III	CMP
18	+	+	–	+	+	+	–	+	+	+	III	CMP + HPT

Fun t l mitral regurgitat n w ls p ese t
Abbreviations JVP = jugular enous p essure PND = paroxysmal nocturnal dyspnea PEP/ET = pre-eject n period/ejecti n time ratio EF = ejection fr tion (by echocard graphy) CT = cardoth racic ratio MR = mit al regurgitati n AR = aortic regu gitation LBBB = complete left bundl branch block MS = mitr l tenosis Unobt = un bta nable CMP = congest ve c rdiomyopathy CAD = coron ry artery disease HPT = hypert nsion.

excluded because the number of beats available for analysis on each echocardiogram (2 or 3) was too small to permit adequate averaging in the presence of arrhythmia In 8 additional subjects the study was abandoned because of our inability to obtain high quality LV echograms in the supine or tilted position

All studies were conducted with the patients in the postabsorptive state on a tilt table in the supine position and after 10 minutes in a 25-degree head up tilted position A foot rest prevented sliding while the muscular effort required on behalf of the examined person to keep his legs extended was minimal at this angle Studies consisted of simultaneous recording of the indirect carotid pulse curve phonocardiogram from the aortic area and LV echocardiogram in both supine and tilted positions Values for the systolic and diastolic blood pressure as measured by sphygmomanometry of the arm were read at the Korotkoff points I and IV respectively and applied to the peak and the onset of upstroke respectively of the indirect carotid pulse curve which was then planimetered to provide the mean blood pressure[2] Echocardiographic studies were performed with the use of an Ekoline 20 diagnostic ultrasonoscope equipped with a 2 25 mega Hz focused transducer (Model C = 12) In 22 cases the echocardiograms were recorded on pictures taken by a Polaroid camera during M mode presentation at a medium sweep velocity that permits completion of a full sweep cycle within 2 seconds and the carotid pulse and the phonocardiogram were independently recorded on a DR 6 photographic recorder † at a paper speed of 100 mm per second with the use of a piezoelectric

"WALK OFF" Ph ical Th py Treatm nt Table Laberne MFG Columbia, S C

Smith Kl n Instruments Palo Alto Calif
†Electronics f r Medicine Wh te Plains N Y

Table I Echocardiographic and other data on 18 normal subjects (Group I) in supine and tilted positions

Patient No	Age (yr)/sex	Position	Dd	Ds	HR	BP (sys/dias/mean)	EDVI	SVI	CI	EF
1	26/M	S	44.5	28.5	79	115/ 70/ 85	47	35	2.8	0.74
		T	40	26.5	89	110/ 80/ 88	34	24	2.1	0.71
2	25/M	S	43.5	31	87	125/ 70/ 88	45	29	2.5	0.64
		T	41.5	29	87	125/ 75/ 93	39	26	2.2	0.6[illegible]
3	15/F	S	41	26	84	115/ 65/ 88	48	36	3.0	0.7[illegible]
		T	32.5	19	84	115/ 65/ 89	24	19	1.6	0.79
4	12/M	S	41	27	72	105/ 75/ 91	66	47	3.4	0.71
		T	36	22	84	105/ 75/ 88	44	34	2.9	0.77
5	8/M	S	36.5	23	82	95/ 65/ 81	52	39	3.2	0.75
		T	32.5	22.5	86	95/ 75/ 88	37	25	2.1	0.68
6	18/F	S	46.5	30.5	74	110/ 70/ 92	71	51	3.8	0.72
		T	38.5	27.5	89	105/ 70/ 84	40	26	2.3	0.65
7	30/M	S	44	30.5	90	120/ 75/ 91	49	33	2.9	0.6[illegible]
		T	43.5	29.5	89	115/ 75/ 89	47	33	2.9	0.[illegible]0
8	9/M	S	37	20.5	82	100/ 50/ 61	51	42	3.5	0.8[illegible]
		T	34.5	20.5	91	105/ 70/ 81	41	33	3.0	0.80
9	18/M	S	53.5	34.5	81	130/ 80/ 95	83	61	4.9	0.73
		T	50	34.5	83	110/ 80/ 90	68	46	3.8	0.68
10	24/M	S	50	33.5	67	130/ 85/ 91	75	52	3.5	0.69
		T	41.5	22.5	75	120/ 80/ 91	43	36	2.7	0.84
11	45/F	S	44	26.5	77	120/ 80/ 95	53	41	3.2	0.7[illegible]
		T	39.5	23.5	82	120/ 80/ 96	38	30	2.5	0.79
12	50/F	S	45	28	77	120/ 75/ 93	64	48	3.7	0.[illegible]5
		T	40.5	27	81	120/ 85/ 98	47	33	2.6	0.70
13	27/M	S	54.5	30	72	100/ 60/ 75	83	69	5.0	0.83
		T	49	28	76	120/ 80/ 95	60	49	3.7	0.82
14	22/F	S	37	23.5	100	135/ 90/108	36	27	2.7	0.75
		T	33	20.5	103	120/ 75/ 94	26	20	2.0	0.[illegible]
15	27/M	S	40.5	21.5	102	125/ 85/103	37	31	3.2	0.84
		T	37	18.5	120	125/ 95/105	28	25	3.0	0.89
16	26/F	S	47.5	29.5	97	115/ 70/ 91	68	52	5.0	0.[illegible]6
		T	43	27.5	97	115/ 80/ 93	50	3[illegible]	3.6	0.[illegible]4
17	42/F	S	46	23.5	86	120/ 80/ 97	55	48	4.1	0.8[illegible]
		T	44.5	24.5	85	125/ 85/101	50	41	3.5	0.8[illegible]
18	42/M	S	47.5	34	83	135/ 85/107	53	34	2.8	0.64
		T	43	27.5	80	135/ 95/109	40	29	2.3	0.72
Mean		S	44.4	27.9	83	118/ 74/ 91	58	43	3.5	0.75
± S E			1.2	1.0	2	3/ 2/ 3	3	3	0.2	0.01
Mean		T	40.0	25.0	88	116/ 79/ 93	42	31	2.7	0.[illegible]5
± S E			1.2	1.0	2	2/ 2/ 2	3	2	0.2	0.01
P			0.01	0.01	0.01	NS / NS / NS	0.01	0.01	0.01	NS

Abbreviations Dd and Ds = echocardiographic end diastolic and end systolic respectively left ventricular internal dimension (mm) HR = heart rate (beats/min) BP = blood pressure sys = systolic dias = diastolic EDVI = left ventricular end diastolic volume index (ml/M) SVI = left ventricular stroke volume index (ml/M) CI = cardiac index (L/min/M) EF = ejection fraction M = male F = female S = supine T = tilted S E = standard error P = level of statistical significance NS = nonsignificant difference in comparison to value in supine position

the clavicle at 45 degree inclination the pre ejection period/ejection time (PEP/ET) ratio was indicative of LV failure if higher than 0.42 a value two standard deviations above the mean[27], the LV ejection fraction (echocardiography) in the supine position and the cardiothoracic (CT) ratio on the upright film were considered to be abnormal if lower or higher, respectively, than 0.50 Four patients (Nos 8 11, Table II) had previously undergone cardiac catheterization the findings of which supported the diagnosis and functional classification Five patients had evidence of mild functional mitral regurgitation All patients were in sinus rhythm Patient No 7 had first degree A V block Because Patients Nos 10 and 16 had complete left bundle branch block the PEP/ET criterion was not employed

Seven patients with rhythm disturbances were

Table III—cont d

Patient No	Age (yr) sex	Position	Dd	D	HR	BP (sys/dias/mean)	EDVI	EF
Group III (congestive heart failure)								
[illegible]	40/M	S	69.5	63.5	103	105/ 8[illegible]/ 90	1[illegible]8	0.24
		T	[illegible]0.5	63	107	10[illegible]/ 90/ 95	186	0.28
8	5[illegible]/M	S	84.5	[illegible]8.5	100	125/ 75/ 95	308	0.[illegible]
		T	84	[illegible]	98	100/ 80/ 86	303	0.[illegible]
9	50/M	S	[illegible]5.5	7[illegible].5	114	9[illegible]/ 60/ 72	268	0.12
		T	[illegible]4.5	[illegible]2	114	90/ [illegible]0/ 63	2[illegible]8	0.10
10	5[illegible]/M	S	83.5	81	10[illegible]	120/100/10[illegible]	399	0.26
		T	90.5	83	10[illegible]	125/105/110	413	0.23
11	46/F	S	56.5	50	80	110/ 75/ 90	14[illegible]	0.31
		T	56	50.5	85	110/ [illegible]/ 91	138	0.27
1[illegible]	5[illegible]/M	S	[illegible]3.5	65.5	80	140/110/1[illegible]	234	0.[illegible]
		T	[illegible]3	64	83	145/110/124	2[illegible]	0.33
13	58/M	S	71	63	84	115/ 85/ 91	24[illegible]	0.30
		T	[illegible]0.5	6[illegible]	84	100/ 80/ 86	240	0.32
14	4[illegible]/M	S	57.5	50.5	84	130/ 95/108	103	0.32
		T	57	50.5	80	130/ 90/104	100	0.30
15	21/F	S	7[illegible]	66	118	100/ 80/ 84	268	0.23
		T	73.5	63	1[illegible]1	9[illegible]/ 80/ 84	28[illegible]	0.37
16	36/M	S	[illegible]6	67	103	95/ [illegible]0/ [illegible]7	261	0.31
		T	[illegible]6	68	104	85/ 65/ 73	261	0.28
1[illegible]	39/M	S	59	52	68	110/ 85/ 96	1[illegible]4	0.31
		T	58	51.5	74	105/ 85/ 9[illegible]	118	0.30
18	52/M	S	65	[illegible]8.[illegible]	10[illegible]	125/100/108	160	0.2[illegible]
		T	67	59	10[illegible]	1[illegible]0/ 9[illegible]/103	1[illegible]5	0.31
Mean		S	[illegible]0.8	64	9[illegible]	114/ 8[illegible]/ 95	224	0.26
± SE			2.9	2.9	4	4 / 4 / 4	25	0.01
Mean		T	[illegible]0.9	63.5	96	109/ 84/ 93	2[illegible]	0.28
± SE			3	2.9	4	5 / 5 / 5	6	0.02
P			NS	NS	NS	NS/ NS/ NS	NS	NS

the depth compensating function of the echocardiograph was permitted

These precautions were directed at preserving the same point of entrance and the same angle of the ultrasonic transducer relative to the chest in both the supine and the tilted positions Since change in position from supine to upright may (theoretically at least) modify the position of the heart within the chest these precautions could not obviously guarantee sampling echoes from the same points of the LV posterior wall and the interventricular septum in both positions therefore casting doubt about the validity of the observed changes in echocardiographic LV dimensions It seemed however that at this angle such change in the position of the heart was insignificant for with three exceptions there was no apparent change in the appearance of the LV echocardiogram and the structures visualized within the LV cavity, immediately upon reaching 25-degree tilt At that moment in 2 cases the echo of the posterior chordae tendineae was replaced by that of the posterior mitral cusp and in 1 case the echocardiographic pattern of the posterior LV wall was replaced by that of the posterior left atrial wall indicating a caudal displacement of the heart these 3 cases were also excluded from the study

Statistical analysis of the results was done on an Olivetti Programma 101 calculator with the use of the Student t test for paired data and the level of statistical significance was set at $P < 0.01$

Results

Representative echocardiograms of the left ventricle in the supine and the tilted positions are shown in Fig 1 for Group I and in Fig 2 for Groups II and III The results are listed in detail in Tables I and III and graphically depicted in Fig 3

Group I (normal subjects) A change from

Table III Echocardiographic and other data on 6 patients with compensated left ventricular volume overloading (Group II) and 12 patients with congestive heart failure (Group III)

Patient No	Age (yr) sex	Position	Dd	Ds	HR	BP (sys/dias/mean)	EDVI	EF
Group II (compensated left ventricular volume overloading)								
1	26/F	S	63.5	41.5	82	120/75/91	176	0.66
		T	59.5	41.5	84	120/75/91	145	0.66
2	48/M	S	68.5	51	64	130/70/88	188	0.59
		T	65	50	64	135/65/93	161	0.57
3	50/M	S	57	43.5	106	145/65/98	139	0.55
		T	53	40	122	140/70/95	105	0.57
4	44/F	S	49.5	35	85	130/85/107	69	0.65
		T	47.5	31	85	115/80/100	61	0.64
5	16/F	S	55.5	34.5	114	115/75/86	105	0.76
		T	52.5	30.5	115	120/70/90	89	0.81
6	24/M	S	68.5	44	89	150/35/69	181	0.73
		T	65	45	89	145/30/63	156	0.67
Mean		S	60.4	42.1	90	132/67/90	147	0.66
± SE			3.1	2.6	7	6/7/5	20	0.03
Mean		T	57.1	40.2	93	129/65/89	119	0.65
± SE			2.9	2.9	9	5/7/5	17	0.04
P			0.01	NS	NS	NS/NS/NS	0.01	NS

Calculated as diastolic pressure plus one third of pulse pressure
Abbreviations are the same as in Table I
The numbers assigned to the patients correspond to those in Table II

transducer manually held over the carotid artery In the 14 remaining cases the LV echogram was relayed to and recorded on a Cambridge physiologic strip chart recorder together with the carotid pulse and the phonocardiogram at a paper speed ranging from 25 to 100 mm per minute The PEP/ET ratio was calculated from measurements on 100 mm/sec recordings and the average value from at least 5 cardiac cycles was used To minimize the effect of respiration on the position of the heart relative to the ultrasonic transducer all echograms were recorded during a passive held expiration

The objective of the echocardiographic study was to identify echoes originating from the endocardium of the left side of the interventricular septum and that of the LV posterior wall in a plane immediately below the mitral valve as previously described by others the vertical distance between these two echoes approximating the LV internal minor axis was measured at the end of diastole (Dd) and end of systole (Ds) in all (2 or 3) cycles available on each Polaroid picture, and in at least 5 cycles on the echograms recorded on the strip chart the average values for Dd and Ds rounded to the nearest 0.5 mm were used to provide an approximation of the LV end diastolic and LV end systolic volume respectively from the formula Volume = $1.047 D^3$ These LV volumes and their difference the stroke volume were then indexed for body surface area End diastole was considered to coincide with the peak of the R wave of the electrocardiogram, end systole was defined as the moment of the peak upward (anterior) motion of the endocardium of the LV posterior wall Ejection fraction was calculated as

$$EF = \frac{(Dd)^3 - (Ds)^3}{(Dd)^3}$$

During the tilt test, specific care was taken by the examiner to avoid false changes in LV dimensions produced by involuntary alterations in either the exact point of application of the ultrasonic transducer on the chest wall or the direction of the ultrasonic beam in relation to the heart To minimize this possibility once the baseline echocardiogram was recorded in the supine position, (1) the examiner's arm holding the transducer was firmly positioned on the chest of the examined person and kept there until the second LV echogram was recorded in the tilted position, and (2) throughout the period between the first (supine) and the second (tilted) LV echocardiograms neither change in the position and angle of the transducer nor modification of the setting of

the compromised venous return to the heart However it seems that these homeostatic negative feedback mechanisms fail to provide full compensation for when a steady state is reached after several minutes the filling pressure end diastolic volume and stroke volume of both ventricles as well as the cardiac output remain lower than the respective baseline values obtained in the supine position [ ] Furthermore the increased venous pressure in the lower half of the body results in a net loss of fluid If the tilted position is prolonged the resulting progressive diminution in blood volume may further compromise the cardiac output to an extent that despite maximal compensation the blood pressure falls to levels incompatible with adequate blood perfusion to the brain and fainting may ensue [ ]

Previous studies have demonstrated a different pattern of response to tilt exhibited by failing hearts Thus the gravitational effect of this intervention on the venous return to the heart is minimal because the expanded blood volume[10] and the increased venous tone existing in cases of heart failure diminish the compliance of the capacitance vessels of the periphery and prevent significant shift of blood to the dependent parts of the body in the tilted position Consequently stroke volume and cardiac output remain practically unaffected by this intervention [ ] whereas blood pressure is maintained at the levels existing in the supine position without significant change in heart rate or the systemic vascular resistance [ ] This hemodynamic response adequately explains the tolerance to orthostatic stress observed in patients with heart failure and also in normal subjects after acute blood volume expansion induced by infusion of normal saline

If allowances are made for differences in the angle and the duration of the tilt our findings concerning the response of heart rate blood pressure stroke volume and cardiac output to this intervention are directionally similar and quantitatively comparable to those reported by others who employed invasive techniques In reviewing the literature however we found only one report concerning the effect of upright tilt specifically on the volume of the normal human left ventricle Data pertinent to the effects of this intervention on the volume of the failing left ventricle are lacking Our data indicate that upright tilt results in a significant decrease in the volume of the normal left ventricle, which finding is in agreement with the findings of Paley and associates [ ] In addition our study examined the volume of the failing left ventricle and found it to be not affected by this intervention Observations on the effect of tilt on the volume of the normal and the failing right ventricle have yielded similar results [ ] Furthermore our findings and those of Paley and associates [ ] suggest that the effect of upright tilt on the stroke volume of both the normal and the failing left ventricle is chiefly determined by the effect of this intervention on the end-diastolic volume of this chamber according to the Frank Starling principle since the ejection fraction was not altered by the tilt

Most patients with compensated heart disease respond to tilt in a manner similar to that observed in normal subjects insofar as the heart rate blood pressure and cardiac output are concerned [ ] and according to our findings in Group II this is also true for the volume of the left ventricle In our Group II the presence of valvular regurgitation precluded determination of the forward stroke volume and minute output of the left ventricle by echocardiography Consequently analysis of the response of these variables to tilt and comparison to the responses exhibited by the normal group are not feasible However the inclusion of Group II in the study was successful in excluding one factor the enlargement of the left ventricle as being responsible for the difference observed between normal and failing hearts with regard to the effect of tilt on left ventricular volume

In this study conclusions concerning left ventricular volume and output are drawn from measurements of a single internal dimension of the left ventricle by means of the cube formula with its attendant assumptions [ ] Although echocardiographic estimates of left ventricular volume by this formula correlate significantly with the corresponding angiocardiographic volume of normal sized left ventricles evidence exists that the assumption of a 2 1 major/minor axis ratio is substantially violated in the case of the enlarged and therefore more spherical left ventricle resulting in an overestimation of its volume [ ] It is also obvious that overestimation of both the end-diastolic and the end systolic volumes by a certain factor would lead to an overestimation of their difference the stroke volume by the same factor Thus calculation of left ventricular stroke

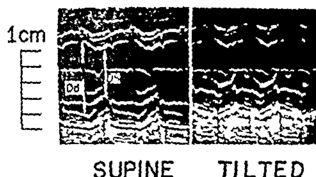


Fig 1 Representative echocardiograms of a normal subject in Group I Note the smaller end diastolic (*Dd*) and end systolic (*Ds*) internal dimensions of the left ventricle in the tilted position

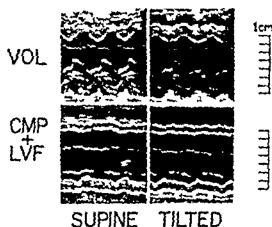


Fig 2 Representative echocardiograms from a patient in Group II with compensated left ventricular volume overload (*VOL*) and from a patient in Group III with left ventricular failure due to congestive cardiomyopathy (*CMP + LVF*) A decrease in left ventricular dimensions in the tilted position is observed in VOL but not in CMP + LVF

supine to tilted position in this group resulted in a significant decrease in Dd (44 4 to 40 0 mm) Ds (27 9 to 25 0 mm), end diastolic volume index (EDVI, by 27 per cent) stroke index (by 27 6 per cent) and cardiac index (by 22 8 per cent) (Table II and Figs 1 and 3)

Group II (compensated LV volume overloading) Transition from supine to tilted position in this group resulted in a significant decrease in Dd (60 4 to 57 1 mm) and EDVI (by 16 per cent) a response similar to that observed in the normal Group I The response of Ds to the tilt was statistically insignificant (42 1 to 40 2 mm) (Table II and Figs 2 and 3)

Group III (congestive heart failure) In contrast to the findings in Groups I and II, a change from supine to tilted position in this group failed to elicit any significant change in the LV dimensions (Dd 70 8 to 70 9 mm Ds 64 to 63 5 mm) The

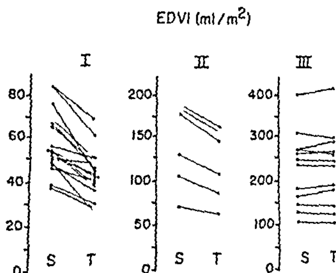


Fig 3 Effect of change from supine (*S*) to upright tilted (*T*) position on the left ventricular end diastolic volume index (*EDVI*) as determined by echocardiography in normal subjects (*I*) patients with compensated left ventricular volume overloading (*II*) and patients with left ventricular failure (*III*)

observed change in the calculated EDVI during tilt was less than 1 per cent of the EDVI in the supine position (Table III and Figs 2 and 3)

With the exception of a small increase in heart rate (83 to 88 beats per minute) observed during tilt in the normal Group I, changes in heart rate ejection fraction and blood pressure were insignificant in all three groups

Discussion

Transition from supine to upright tilted or erect posture is known to elicit a sequence of events that constitute the characteristic hemodynamic response of the normal heart to this intervention Thus upright tilt favors a shift of blood into the venous reservoir of the lower half of the body below the heart level[7, 31] thereby diminishing the gradient for venous return to the heart resulting in a decrease in the filling pressure[4, 6, 11, 34] end diastolic volume[20] and stroke volume[4, 20] of the right ventricle As one might expect, the end diastolic volume,[21] stroke volume[2, 4, 21, 31, 34] and minute output[1, 4, 32, 34] of the left ventricle subsequently decline, and the resulting sympathetic activation mediated by the baroreceptors[35, 36] prevents a fall in blood pressure This is brought upon by (1) increasing the heart rate[1, 3, 7, 20, 31, 34] to counterbalance the effect of a diminishing stroke volume on the cardiac output, (2) increasing the arteriolar tone, thus raising the systemic vascular resistance[3, 4], and (3) increasing the venous tone[31] thus improving

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and cardiac index in Group III would yield values unacceptably high for hearts in severe failure these values are therefore omitted from Table III as being misleading However since in Group III upright tilt failed to change the dimensions of the left ventricle, equal overestimation of stroke volume should be present in both supine and tilted positions Therefore the statement that the end diastolic and stroke volume of the left ventricle remained unaltered during tilt is valid despite our inability to calculate the true values of these variables Similarly equal overestimation between stroke volume and end diastolic volume in the large hearts of Groups II and III would leave their ratio the ejection fraction unaffected thus permitting valid conclusions concerning the response of this variable to upright tilt

Acceptance of the observed changes in left ventricular dimensions as representing true changes in volume requires the assumption that change from supine to 25 degree upright tilted position does not modify significantly the geometry of the left ventricle as expressed in its major/minor axis ratio Although not tested in this study in which only one left ventricular dimension could be monitored this assumption was accepted on account of the following considerations

1 The decrease in left ventricular end diastolic volume stroke volume and cardiac output observed during tilt in our normal Group I was practically similar to that reported by Paley and associates [1] on 6 normal subjects if allowance is made for the different tilt angle employed in their study in which left ventricular volume and output were determined by techniques not dependent on any assumption concerning the geometry of the left ventricle

2 The effects of tilt on left ventricular volume and output calculated on the basis of this assumption in Groups I and III were those anticipated from extrapolation of results of similar studies concerning the volume and output of the normal and the failing right ventricle respectively [20]

3 If the observed decrease in left ventricular dimension in our normal Group I was due to a change in left ventricular geometry induced by the tilt Group III should have exhibited a similar response, however, such a response was not observed Obviously this discrepancy cannot be accounted for by the presence of left ventricular enlargement in Group III for abnormally enlarged but nonfailing hearts of Group II responded to tilt in a normal fashion

In conclusion, this study has shown that transition from the supine to the upright tilted position diminishes the volume and output of the normal but not the failing left ventricle In view of the normal response exhibited by the enlarged but nonfailing hearts, our data support the hypothesis that the hemodynamic effect of this intervention is not dependent upon the magnitude of LV volume preload but rather upon the existence or nonexistence of left ventricular failure and its consequences on the peripheral circulation

Summary

The effect of a passive change from supine to 25 degree head up tilted position on left ventricular volume was studied by echocardiography and other noninvasive techniques in 18 normal subjects 6 patients with compensated LV volume overloading and 12 patients with LV failure In normal subjects and patients with compensated LV volume overloading 10 minutes of head up tilt resulted in a significant decrease in the echocardiographic LV internal dimension equivalent to a decrease in the calculated LV end diastolic volume of 27 and 16 per cent respectively In contrast no change in LV end diastolic dimension and volume was noted during tilt in the patients with LV failure The response of heart rate blood pressure and LV ejection fraction to this intervention was insignificant in all groups These data indicate that volume preload is unresponsive to postural changes in patients with LV failure but not in normal subjects or in those with compensated LV volume overloading It is suggested that the effect of posture on LV volume and output is primarily determined by the absence or presence of LV failure and the consequences of it on the peripheral circulation

We wish to extend our appreciation to the medical students and other persons who volunteered in this study We also acknowledge the excellent technical assistance of Mrs Beryl Wilson and the secretarial help of Mrs Frances Hensley and Mrs Kitty Brittingham

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Table I WPW–procaine amide study

Patient	Age and sex	WPW type	Total PA dose (mg)	Δ vector eliminated how long?	Tach (rate) pre/post	Max 1:1 atrial pacing rate		AV refractory periods effective/functional		VA refractory periods effective/functional		VA conduction time		Max 1:1 vent pacing rate	
						pre	post	pre	post	pre	post	pre	post	pre	post
J A	53 F	I	500	+/−	170/none No Δ	200 Δ	200 Δ	291/275	243/247						
J R	42 M	I	00	Yes 1 hr	227/none No Δ	150 No Δ	215 No Δ	280/239	283/330						
G G	57 F	A	600	Yes 1 ½ hr	150/none No Δ	150 Δ/RSR	150 RSR	306/318	301/408						
M F	44 F	A	500	Yes 30 min	177/none No Δ	1 0 No Δ	1 0 No Δ	338/400	3 1/495						
M M	50 F	I	450	Yes, 30 min	1 1/177 No Δ No Δ	195 No Δ	170 No Δ	270/270	276/391						
A H	61 M	A	750	+/−	none/none	190 Δ	170 Δ	288/370	3 0/368			250	308	190	110
S G	49 F	A	400	Yes 2 hr	150/145 No Δ No Δ	150 No Δ	170 No Δ	310/430	34 /400	260/3 8	235/360	175	210	210	200
H P	45 M	I	400	Yes 30 min	none/none	130 No Δ	130 No Δ	393/393	310/445	330/345	351/415	140	184	200	150
J J	49 M	A	850	Yes 1 hr	none/none	210 Δ	150 No Δ	299/345	310/450			none			
W E	54 M	A	850	Yes 2 hr	170/none No Δ	190 Δ	150 No Δ	290/400	393/430	360/430	410/425	230	250	200	130
D R	13 M	A	550	Yes 8 ½ hr	143/150 No Δ No Δ							210	223	150	150
H Y	46 M	A	1 600	Yes, 30 min	152/none No Δ	190 Δ	1 0 No Δ	340/360	310/410	360/380	VA Block	305	none	190	–
M K	42 M	B	1 000	+/−	none	290 Δ	150 No Δ	295/300	300/360	240/255	340/345	115	130	210	90

amide (10 mg per kilogram) by intravenous infusion at a rate of 35 mg per minute Peripheral arterial pressure was continuously monitored Statistical evaluation was performed with Student's t test for paired samples Data were expressed as mean values ± standard error of the mean

Results

A Effect of procaine amide on the delta wave

In the resting state all 13 patients had persistent delta waves Following termination of the procaine amide (PA) infusion the delta wave disappeared in 10 and was modified in three of the remaining patients (Table I) as determined by lengthening of P Δ interval and shortening of QRS duration No change in P wave duration or morphology was observed In six of the 10 patients the delta wave disappeared after the infusion of 200 mg of procaine amide In the 10 patients whose delta wave disappeared it reappeared between 30 minutes and 8 hours the time of reappearance of the delta wave was not related to the total dose of procaine amide administered (Table I) At this point in time blood levels would be estimated to be 2 to 4 mg per liter [25]

B Atrial pacing studies

Control In 12 of the 13 patients atrial pacing could be satisfactorily performed at increasing rates until anterograde conduction block occurred Six patients who maintained a delta wave to the point of anterograde block had a maximum atrial pacing rate (maximal atrial pacing rate is defined as the highest achieved atrial pacing rate with 1 1 A V conduction rates above this level result in A V block) with 1 1 A V conduction of 200 ± 5 2 beats per minute (mean ± S E M) (Fig 1 A Table I) In contrast in the six patients without a delta wave at the point of maximum atrial pacing the rate with 1 1 A V conduction

The Wolff-Parkinson-White syndrome
Pharmacologic effects of procaine amide

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Michael M Laks M D
Kanji Obayashi M D
Hirokazu Hayakawa M D
William Daley
Los Angeles Calif

Wolff Parkinson and White[1] in 1930 described a clinical syndrome consisting of shortened P R interval, widened QRS delta wave and a history of tachycardias In the past 10 years with the recent advances in pacing techniques and the capability of recording intracardiac electrograms numerous studies have been reported describing the electrophysiologic features of the Wolff Parkinson White syndrome[2-11] Furthermore, the recent studies which related the sequence of activation determined by epicardial mapping to the site of anatomic bypass tract(s) have significantly improved our knowledge of the pathophysiology of arrhythmias in this syndrome[11-17] In spite of this progress, a rational pharmacologic treatment for patients with the Wolff Parkinson White (WPW) syndrome has not been attained because of the limited number of combined electrophysiological and pharmacological studies of the various drugs used in the therapy of arrhythmias in this syndrome[18-22] Therefore the purpose of this study was to determine the electrophysiologic effects of the commonly used antiarrhythmic agent procaine amide in patients with the WPW syndrome

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Methods

Thirteen patients who had classic electrocardiographic features of the WPW syndrome with recurrent tachyarrhythmias were studied after obtaining informed consent The patient age range was from 13 to 57 with eight males and five females (Table I) All studies were performed in the postabsorptive state, patients had not received any medication for a minimum of 48 hours prior to study Intracardiac electrogram recordings were obtained with standard techniques[23] All equipment was adequately grounded and isolation units used to insure leakage current equal to or less than 10 microamps Electrograms were recorded on a multichannel photographic recorder with paper speeds between 25 and 100 mm per second * Atrial pacing was performed at rates from 90 to 250 per minute, while standard electrocardiographic Leads I, II, and III as well as high right atrial (AEG) and His bundle electrograms (HBE) were recorded In addition, utilizing the extrastimulus technique with atrial pacing at a rate of 90 per minute[24] atrioventricular (A V) refractory periods were measured Ventricular pacing was subsequently performed at increasing heart rates from 90 to 210 per minute to assess V A conduction time Finally V A refractory periods were obtained by the extrastimulus technique with a high right atrial recording and stimulation of the right ventricular apex

The electrophysiologic studies described were repeated after the administration of procaine

*Electronics for Medicine Model DR 12

Table I WPW-procaine amide study

Patient	Age and sex	WPW type	Total PA dose (mg)	Δ vector eliminated how long?	Tach (rate) pre/post	Max 1:1 atrial pacing rate		AV refractory periods effective/functional		VA refractory periods effective/functional		VA conduction time		Max 1:1 vent. pacing rate	
						pre	post	pre	post	pre	post	pre	post	pre	post
J.A.	?3 F	I	500	+/–	1?0/none No Δ	200 Δ	200 Δ	?91/??5	243/247						
J.R.	4? M	I	?00	Yes 1 hr	22?/none No Δ	150 No Δ	21? No Δ	?80/233	283/330						
G.G.	57 F	A	600	Yes 1¼ hr	150/none No Δ	150 Δ/RSR	150 RSR	306/318	301/408						
M.F.	44 F	A	500	Yes 30 min	1?7/none No Δ	1?0 No Δ	170 No Δ	3?8/400	361/49?						
M.M.	50 F	I	450	Yes 30 min	171/1?7 No Δ No Δ	19? No Δ	1?0 No Δ	2?0/??0	?76/3?1						
A.H.	61 M	A	?50	+/–	none/none	190 Δ	1?0 Δ	288/3?0	3?0/368			250	308	190	110
S.G.	49 F	A	400	Yes 2 hr	150/145 No Δ No Δ	150 No Δ	170 No Δ	310/430	34?/400	260/3?8	23?/360	1?5	210	210	200
H.P.	45 M	I	?00	Yes 30 min	none/none	130 No Δ	130 No Δ	393/393	310/445	330/34?	3?1/415	140	184	?00	1?0
J.J.	49 M	A	850	Yes 1 hr	none none	210 Δ	150 No Δ	289/345	310/450			none			
W.E.	54 M	A	850	Yes 2 hr	1?0/none No Δ	190 Δ	150 No Δ	290/400	3?3/430	360/430	410/42?	2?0	2?0	200	130
D.R.	13 M	A	550	Yes 8½ hr	143/150 No Δ No Δ							210	223	150	1?0
H.Y.	46 M	A	1600	Yes 30 min	152/none No Δ	190 Δ	150 No Δ	340/360	315/410	360/380	VA Block	30?	none	190	--
M.K.	4? M	B	1000	+/–	none	2?0 Δ	150 No Δ	29?/?00	305/360	?40/2??	340/345	115	130	?10	90

amide (10 mg per kilogram) by intravenous infusion at a rate of 35 mg per minute Peripheral arterial pressure was continuously monitored Statistical evaluation was performed with Student's t test for paired samples Data were expressed as mean values ± standard error of the mean

Results

A. Effect of procaine amide on the delta wave

In the resting state all 13 patients had persistent delta waves Following termination of the procaine amide (PA) infusion the delta wave disappeared in 10 and was modified in three of the remaining patients (Table I) as determined by lengthening of P Δ interval and shortening of QRS duration No change in P wave duration or morphology was observed In six of the 10 patients the delta wave disappeared after the infusion of 200 mg of procaine amide In the 10 patients whose delta wave disappeared it reappeared between 30 minutes and 8 hours the time of reappearance of the delta wave was not related to the total dose of procaine amide administered (Table I) At this point in time blood levels would be estimated to be 2 to 4 mg per liter [2?]

B Atrial pacing studies

Control In 12 of the 13 patients atrial pacing could be satisfactorily performed at increasing rates until anterograde conduction block occurred Six patients who maintained a delta wave to the point of anterograde block had a maximum atrial pacing rate (maximal atrial pacing rate is defined as the highest achieved atrial pacing rate with 1 1 A V conduction rates above this level result in A V block) with 1 1 A V conduction of 200 ± 5 2 beats per minute (mean ± S E M) (Fig 1 A Table I) In contrast in the six patients without a delta wave at the point of maximum atrial pacing the rate with 1 1 A V conduction

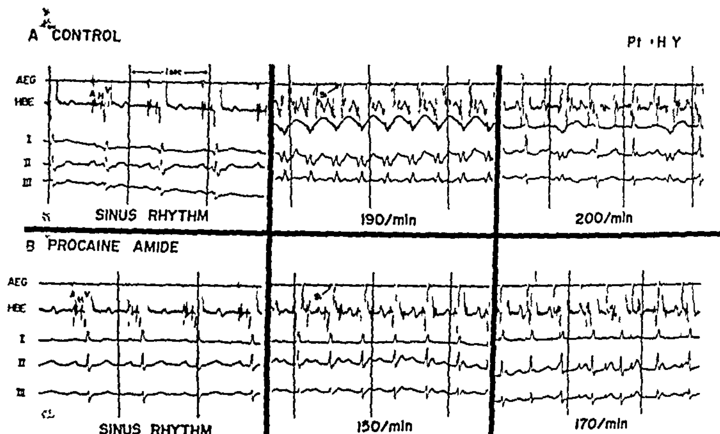


Fig 1 The effect of increasing right atrial pacing rates on A V conduction in the WPW syndrome Panel *A* shows the results obtained in the control state The far left panel shows the tracing obtained in sinus rhythm The traces are from above downward the high right atrial electrogram (AEG) the His bundle electrogram (HBE) and standard ECG Leads I II and III A H and V signify the low right atrial His and ventricular depolarizations A 1 sec time calibration is also identified Note the prominent initial QRS deformity (delta wave) The middle panel shows a record obtained during pacing at the highest rate (190 per minute) with 1 1 A V conduction S signifies the stimulus artifact The far right panel shows the response during pacing at 200 per minute anterograde block is observed in both the bypass and the normal A V conduction system Panel *B* shows a similar sequence in the same patient (H Y) following procaine amide administration Note the absent delta vector and the development of anterograde A V nodal block at 170 per minute

was 157 5 ± 9 1 beats per minute ($p < 0\,01$)

Procaine amide In four of the six patients in whom the delta wave persisted to the point of maximum atrial pacing in the control state and eliminated with procaine amide procaine amide produced a lesser maximum atrial pacing rate with 1 1 A V conduction (PA, 150 0 ± 1 2 beats per minute control 202 5 ± 7 5 $p < 0\,005$) (Fig 1 *B*) In the six patients who had no delta wave at the point of maximum atrial pacing in the control state procaine amide resulted in no statistically significant change in the maximum atrial pacing rate with 1 1 A V conduction (PA, 167 5 ± 11 5 beats per minute control 157 5 ± 9 1, $p > 0\,05$)

C Ventricular pacing studies

Control

A V A Refractoriness Apical right ventricular pacing at increasing rates was performed in eight of the 13 patients to assess V A refractoriness and conduction The maximum pacing rate with 1 1 V A conduction was 192 8 ± 7 8 beats per minute (range 150 to 210 per minute) V A conduction time did not change in seven patients at pacing rates from 90 to 210 per minute (Fig 2, 4 Table I) V A conduction was absent in one patient (J J) The mean V A conduction time was 203 6 ± 24 8 msec (range 140 to 305 msec)

B Relationship Between Bypass Site and V A Conduction Time The different V A conduction times were related to the anatomic bypass site as estimated by the delta wave direction determined from the standard electrocardiogram Patients with right atrial to right ventricular bypass tracts had V A conduction times from 115 to 175 msec, whereas patients with left atrial to left ventricular bypass tracts had V A conduction times from 210 to 305 msec (Table II)

Procaine amide Following procaine amide infusion, V A conduction time increased in six patients (PA 217 5 ± 24 6, control 186 7 ± 21 5)

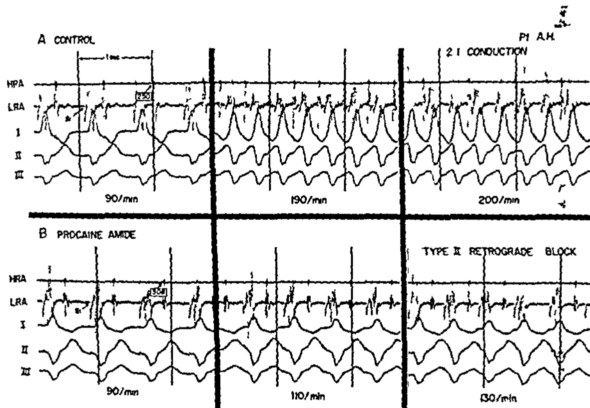


Fig 2 The effect of increasing right ventricular pacing rates on V A conduction in the WPW syndrome Panel *A* shows the results obtained in the control state The far left panel shows the results obtained at a pacing rate of 90 per minute S identifies the stimulus artifact The traces are from above downward a high right atrial electrogram (HRA) a low right atrial electrogram (LRA) and standard ECG Leads I II and III The number within the small box identifies the retrograde conduction time A 1 sec time calibration is also indicated. The middle panel shows a record obtained at the most rapid pacing rate (190 per minute) with 1 1 V A conduction The far right panel shows the result of increasing the pacing rate to 200 per minute 2 1 V A conduction occurs Panel *B* shows the results obtained in the same patient (A H) following procaine amide infusion Note the increase in V A conduction time to 308 msec and the development of type II retrograde block at a rate of 130 per minute

($p < 0.005$) (Fig 2 *B* Table I) V A conduction was absent in the remaining two patients The V A conduction time did not change with increasing pacing rates in all the patients In the six patients with intact V A conduction the maximum pacing rate with 1 1 V A conduction decreased from 193 3 ± 9 2 (control) to 138 3 ± 15 6 beats per minute (PA) ($p < 0.05$)

D Atrial vs ventricular pacing

Control In a subgroup of six patients studied maximal pacing rates to the point of block were not significantly different from the atria (178 3 ± 13 2 beats per minute) as compared to pacing from the ventricle (200 5 ± 3 7 beats per minute) (NS) (Table I) Of interest in the two patients without delta waves a significantly higher maximum 1 1 pacing rate occurred during ventricular (205 per minute) than atrial pacing (140 per minute)

Procaine amide In a subgroup of five patients, procaine amide did not significantly change the rate of maximum atrial pacing (control 176 0 ± 16 beats per minute PA 154 0 ± 7 5 beats per minute [NS]) In contrast procaine amide significantly altered the maximum ventricular pacing rate (control 202 0 ± 3 7 beats per minute PA 134 0 ± 19 7 beats per minute) ($p < 0.05$) (Table I)

E Effects of progressively premature atrial depolarizations

Control In 12 of the 13 patients consistent progressively premature atrial depolarizations could be electrically induced Two types of responses were observed from plotting atrial test coupling intervals (A_1 A_2 interval in milliseconds) to the His bundle or ventricular response (H_1 H_2 and/or V_1 V_2 interval in milliseconds) (1) points plot curvilinearly as described by Wit and associates [4] as a type I curve indicating at least A V nodal conduction (2) points plot on the line of

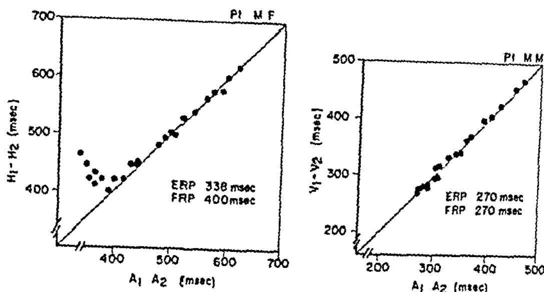


Fig 3 A V refractory period measurements in patients with the WPW syndrome On the horizontal axis are plotted the A A intervals in milliseconds and on the vertical axis are plotted the H H (left panel) or the V V, (right panel) intervals The left hand panel shows a type I response effective (ERP) and functional (FRP) refractory period measurements are indicated The right hand panel shows a line of identity response with refractory period measurements indicated

Table II Relationship between V A conduction and suspected bypass site

Patient	V A conduction time (msec)	Δ Vector F/T	Suspected bypass site
A H	250	+90 / +80	Post lat LV
S C	175	−40 / +50	Post RV septum
H P	140	+75 / +40°	Post RV
W E	230	+110 / +95	Post lat LV
D R	210	95 / +80	Post lat LV
H Y	305	+30 / +50	Lat LV †
M K	115	−20 / +15	P [illegible] RV

The delta vector was expressed as degrees in the front[illegible] and [illegible] transverse plane (T)
†Patient H Y was extremely obese (160 kilogram) thereby tempering our observations with regard to the bypass site relative to a shift in the cardiac position within the thorax

identity indicating at least bypass tract conduction (Fig 3) Six patients with a type I curve had mean effective refractory periods of 299 2 ± 8 7 msec and a functional refractory period of 370 7 ± 18 4 msec Six patients with line of identity (LI) response had a mean refractory period of 315 8 ± 18 0 (Table I) In all these six LI patients the delta wave was present at all coupling intervals in the test beat (A) Furthermore H depolarizations were not readily identifiable

Procaine amide Following infusion of procaine amide eight patients who had their delta waves blocked underwent repeat studies In this group four of the eight subjects had type I curves in the control period and all eight had type I curves after procaine amide In the four patients with a type I response before (control) and after procaine amide the effective refractory periods were control 304 5 ± 12 8 msec PA 328 0 ± 16 9 msec (NS) (Table I)

F Comparison of the refractory periods as determined by maximum atrial pacing and atrial premature depolarization methods

Control In four patients who had line of identity responses and persistent delta waves with atrial pacing the shortest cycle length before anterograde block was 322 0 ± 27 4 msec In these same patients the effective refractory period as measured by the atrial premature depolarization method was 308 0 ± 11 1 msec (NS) In the three patients who had type I responses and absent delta waves during maximal atrial pacing a large but not statistically significant difference was observed between the effective refractory period as measured by atrial premature depolarizations (309 3 ± 16 7 msec) and the maximum pacing rate cycle length (384 3 ± 15 7 msec) (Table I)

Procaine amide In nine patients with blocked delta waves following procaine amide infusion, the shortest cycle length during atrial pacing with 1 1 A V conduction was 377 8 ± 16 9 msec as compared to the effective refractory period (313 8 ± 9 0) ($p < 0.01$) obtained by the extrastimulus method In the four patients with type I response in both the control state and following procaine

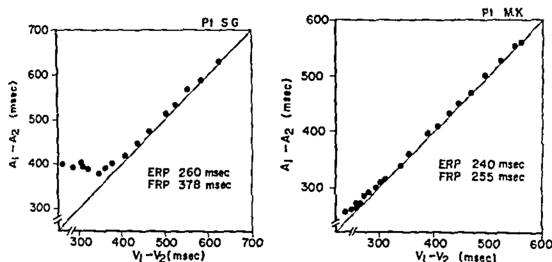


Fig 4 VA refractory period measurements in patients with the WPW syndrome On the horizontal axis are plotted the V V intervals in milliseconds and on the vertical axis are plotted the A A responses in milliseconds. The left hand panel shows a type I response with the effective (ERP) and functional (FRP) refractory period measurements indicated. The right hand panel shows a line of identity response with the ERP and FRP values (for the bypass tract) indicated

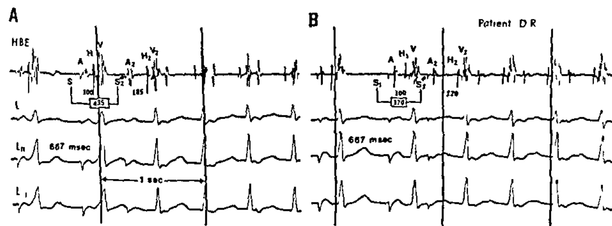


Fig 5 Induction of supraventricular tachycardia (SVT) in a patient with the WPW syndrome Panel *A* shows the induction of SVT in the control state The traces are from above downward the His bundle electrogram (HBE) and standard ECG Leads I II and III A 1 sec time calibration is also indicated S and S indicate the basic (S) and premature (S) stimuli A H and V indicate the basic beat intervals and A H and V indicate the premature beat intervals At a test cycle length of 435 msec (see box) a basic beat A H interval of 100 and a premature beat A H interval of 185 msec are noted The delta wave is absent in the premature beat and a sustained SVT is induced no delta waves are seen during the tachycardia. Panel *B* shows the results obtained after procaine amide infusion Note the absence of a delta wave At an S S interval of 370 msec (see box) an A H interval of 220 msec is observed with resultant SVT

amide the A V nodal effective refractory period as measured by the extrastimulus method was 304 5 ± 12 8 msec (control) and 328 0 ± 16 9 msec (PA) respectively (NS) whereas the maximum pacing cycle length in milliseconds was 367 0 ± 20 6 (control) and 346 2 ± 25 0 (PA) respectively (NS) (Table I)

G Effects of progressively premature ventricular depolarizations

Control In five patients coupled premature ventricular depolarizations were utilized to obtain V A refractory period measurements Plotting $V_1 V_2$ intervals against A A intervals resulted in a line of identity response in three

patients and a type I curve in two patients The mean effective refractory periods for the line of identity group and type I group were identical 310 msec (Fig 4 *A* and *B* Table I)

Procaine amide Following procaine amide infusion V A conduction was blocked in one patient who had line of identity response in the control state In the remaining four patients the mean refractory period did not significantly change (control 297 5 ± 28 4 msec PA, 334 0 ± 36 4 msec [NS]) (Table I) In addition the pattern of V A conduction was altered in two patients with the development of a line of identity response in one and type I curve in the other patient

H Comparison of the refractory periods as determined by maximum ventricular pacing and ventricular premature depolarization methods In the three patients with line of identity responses the retrograde effective refractory period obtained by the extrastimulus method was 310 0 ± 36 1 msec as compared to the cycle length of the maximum ventricular pacing rate in milliseconds of 303 3 ± 11 7 (NS) In the two patients with type I retrograde responses the effective refractory period obtained by the extra stimulus method was 310 0 ± 50 0 as compared to the cycle length of the maximum ventricular pacing rate in milliseconds of 292 5 ± 7 5 (NS) There was no significant difference between the two groups

I Tachycardia induction

Control Tachycardias were induced by premature right atrial depolarization in nine of the 13 patients in all patients the tachycardia was initiated by anterograde bypass block (Fig 5 *A*) The mean rate of supraventricular tachycardia was 167 2 ± 7 9 beats per minute (range 143 to 222) delta waves were absent in all patients during the episode of supraventricular tachycardia (Table I)

Procaine amide Tachycardias could be induced in three of the 13 patients following procaine amide infusion although procaine amide blocked the delta wave in these three patients (Fig 5 *B*) The tachycardia rate in these three patients was 154 7 ± 8 4 beats per minute (control 157 3 ± 9 9 beats per minute (NS) (Table I)

Discussion

Procaine amide has been demonstrated to be a highly effective agent in the treatment of arrhythmias of various types [1] Nevertheless a variable and somewhat unpredictable response has been observed in our patient group with the WPW syndrome In this study although the amount of procaine amide administered was determined by the patient's body weight the response on the bypass tract as determined by changes in the delta wave was highly variable In six patients the delta wave was quite sensitive to procaine amide in that it was blocked after an infusion of only 200 mg This variability in response to procaine amide emphasizes the clinical pharmacological maxim A dose response curve must be performed on an individual patient In the patients studied, the delta vector remained blocked for a period ranging from 30 minutes to 8 hours This variable response could not have been predicted from the known pharmacokinetics of procaine amide [9,10] This unpredictability is emphasized by patient H Y, his delta vector was blocked for the shortest period of time in spite of the fact that he was given the largest dose of procaine amide (1600 mg) with a predicted peak serum level of 16 mg per liter This variability of response might be explained by a difference in the degree of binding of procaine amide by the bypass cells This observation serves to re emphasize the importance of having a bioassay system the delta wave serves as the biological indicator of bypass tract conduction

Atrial pacing has been used to evaluate refractoriness of the bypass tract and the normal A V conduction system in patients with the WPW syndrome [2, 11] However in most cases A V nodal and bypass refractoriness cannot be determined in the same patient by atrial pacing This limitation exists because the bundle of His deflection is frequently located within the pre excitation wave and therefore cannot be readily identified The problem of identification is made more difficult because atrial pacing prolongs the AH interval resulting in the His deflection merging with the pre excitation wave Therefore a comparison of the refractory periods of the bypass and A V node can be made only between groups of patients with delta waves indicating anterograde conduction predominantly through the bypass tract and patients without delta waves indicating conduction through the A V node

In our study of six patients with persistent delta waves during atrial pacing anterograde bypass refractoriness was significantly shorter

than anterograde A V nodal refractoriness as determined in the other six patients without persistent delta vectors Of note A V nodal refractoriness in the latter six patients was the same as observed in patients with normal A V nodes without the WPW syndrome[21] Neverthe less atrial pacing does not usually permit defini tion of the refractory period of both the A V node and the bypass tract in the same patient In patients with delta waves in the control state and eliminated by procaine amide a significant reduc t on in the maximum atrial pacing rate with 1 1 A V conduction was observed This would suggest that in this group of patients bypass refractori ness was substantially shorter than A V nodal refractoriness Of importance, this concept is dependent on the observation that procaine amide does not significantly affect A V nodal refractoriness This point was strengthened by the observation that procaine amide did not alter A V nodal refractoriness in six patients who did not have a delta wave Therefore in the doses utilized procaine amide administration was a means of measuring both anterograde A V nodal and anterograde bypass refractoriness in the same patient

Ventricular pacing allows for the assessment of retrograde A V nodal and/or bypass conduction In patients studied fixed V A conduction time occurred regardless of the pacing rate As reported by Wellens and Durrer this suggests dominant retrograde conduction via the bypass tract(s) In our patients procaine amide produced a significant prolongation of V A conduction time as well as a marked reduction of the maximum ventricular pacing rate with 1 1 V A conduction However at the same time five of these seven patients had blocked anterograde bypass conduc tion This study demonstrates a dissociation of the effects of procaine amide on anterograde and retrograde conduction Of importance a disparity exists between anterograde and retrograde con duction and refractoriness in the control state In two patients delta vectors were absent at the maximal atrial pacing rate indicating there was A V nodal conduction However at an even higher ventricular pacing rate there was a fixed V A conduction time indicating retrograde bypass conduction Furthermore one patient had no retrograde conduction in the presence of a per sistent delta wave with rapid atrial pacing These results support the concept described in patients with advanced A V block, that a significant disparity exists between anterograde and retro grade conduction[33, 4]

Anterograde refractory period measurements obtained from line of identity responses identify the bypass tract refractory period Of interest no significant difference between refractory period of the bypass tract and the effective refractory period of the A V node was observed in these two patient groups in the control state Procaine amide blocked the bypass tract as demonstrated by the absence of delta waves and the conversion of a line of identity curve to a type I curve However no significant change in A V nodal refractoriness was observed Therefore in the therapeutic dosage range used procaine amide did not significantly depress A V nodal conduc tion This is in concert with the observation that in man procaine amide does not significantly affect A V nodal transmission time[35]

The two methods used in this study to measure A V nodal conduction and refractoriness were (1) rapid atrial pacing to the point of blocked conduction to the ventricular and (2) progres sively premature atrial depolarizations The re fractory periods of the A V node determined by these techniques need not be the same rapid atrial pacing may alter A V nodal function to a greater extent than premature atrial depolariza tions resulting in a greater determined refractory period This concept was demonstrated in this study by the observation that the A V nodal effective refractory period was longer by the rapid atrial pacing method than by the premature atrial depolarization method In contrast the effective refractory period of the bypass tract as determined by these two methods was the same This observation is consistent with the concept that the bypass tract reacts like myocardial tissue in that the refractory period is not lengthened but may actually be shortened by increasing rate of stimulation[3]

As observed with progressively premature atrial stimuli similar stimulation sequences in the ventricle produced two types of responses as determined by plotting the V_1V_2 intervals versus A A intervals (1) line of identity response or (2) type I response As previously discussed the line of identity response indicates bypass conduction A V nodal conduction may or may not be present Of importance retrograde A V nodal conduction cannot be determined by the methodology used in

patients with line of identity responses In contrast a type I curve suggests predominant retrograde conduction via the normal V A conduction pathways Nevertheless, because of the existence of at least dual pathways, determination of the retrograde refractory period of the individual tracts cannot readily be accomplished However Wellens and Durrer[11] have described cases of WPW in which the A V node area was transsected at surgery, enabling determination of retrograde bypass refractoriness Since procaine amide selectively blocks bypass conduction more than A V nodal conduction, the use of procaine amide may be considered the pharmacologic counterpart of differential surgical intervention

The question of whether procaine amide has a differential effect on anterograde and retrograde refractoriness was posed in this study In two patients procaine amide produced anterograde block in the bypass (delta wave disappeared, type I A V refractory period response occurred) while retrograde bypass conduction was maintained (line of identity response occurred) Therefore, at this dose of procaine amide re entrant arrhythmias still could be produced utilizing the bypass tract in a retrograde fashion This observation is of great clinical importance in that the delta wave present in the surface electrocardiogram cannot be used as an index for successful pharmacologic therapy for tachyarrhythmia prevention

The induction of supraventricular tachycardia in nine of the 13 patient studies is consistent with recent observations utilizing long term electrocardiographic monitoring that tachyarrhythmias are frequent in patients with WPW syndrome[15] Of interest the three patients in whom tachyarrhythmias could not be induced by the premature atrial depolarization method had only infrequent arrhythmias Consequently, this electrophysiologic method appears to be of value as a means of objectively assessing the frequency of tachycardias in this syndrome

The extremely rapid ventricular rates seen in patients with the WPW syndrome occur with atrial fibrillation and not with atrial tachycardia Our observation is consistent with this concept since the rate of induced atrial tachycardia in the WPW syndrome (167 beats per minute) was similar to the rate observed in patients with atrial tachycardia without WPW (161 beats per minute)[10] The different ventricular rates produced in patients with atrial fibrillation and atrial tachycardia are explained by the concept that atrial tachycardia is a reentry mechanism requiring a critical size and refractoriness of the reentry loop while atrial fibrillation consists of a direct rapid electrical bombardment of the bypass tract

Clinical implications Pharmacologic treatment of arrhythmias in patients with the WPW syndrome requires detailed evaluation of the electrophysiologic properties of both the A V node and bypass tract The usual direction of the reentrant loop in supraventricular tachycardia in the WPW syndrome is anterograde A V nodal and retrograde bypass conduction In this case blocking anterograde bypass conduction with procaine amide (loss of the delta wave on the surface ECG) may not prevent tachyarrhythmias However, as measured by intracardiac recording techniques significant prolongation of retrograde bypass conduction by procaine amide is essential for elimination of tachycardias due to this form of re entrant loop

In the rare type of re entrant arrhythmia seen in the WPW syndrome anterograde conduction occurs across the bypass and retrograde conduction occurs across the A V node resulting in a tachycardia with a wide QRS Elimination of anterograde bypass conduction (loss of the delta wave on the surface ECG) would be indicator of appropriate procaine amide drug effect Of special interest is atrial fibrillation, an arrhythmia in which a re entrant loop is probably not an important mechanism for the production of a rapid ventricular rate Therefore, for successful anti arrhythmic drug effect in patients with WPW syndrome and atrial fibrillation procaine amide must be utilized in a dose adequate to produce antegrade bypass block in order to prevent ventricular fibrillation

Finally since procaine amide administration either eliminated or modified the delta vector, this drug has clinical usefulness in (1) the diagnosis of possible cases of WPW and (2) the evaluation of occult ECG abnormalities in patients with the WPW syndrome

Summary

The effect of procaine amide, 10 mg per kilogram via intravenous infusion was studied in 13 patients with the WPW syndrome The delta wave was eliminated by procaine amide in 10 and modified in three patients This effect lasted

between 30 minutes and 8½ hours and was unrelated to the total dose administered Anterograde A V conduction was assessed by atrial pacing with increasing rates More rapid atrial pacing rates with 1 1 A V conduction were observed in patients who maintained rather than lost their delta wave during pacing Ventriculoatrial conduction was assessed with ventricular pacing at increasing rates ventricular conduction time was fixed regardless of the pacing rate Procaine amide significantly prolonged V A conduction time in six and blocked V A conduction in one patient In addition A V and V A refractory periods were measured by the extrastimulus technique Two types of responses were observed (1) Type I or (2) line of identity A V nodal refractoriness was observed to be within the normal range Procaine amide converted antero grade line of identity responses to Type I responses in all patients who had their delta waves eliminated In this patient group bypass refractoriness was shorter than A V nodal refractoriness Procaine amide was not observed to alter significantly normal A V conduction as assessed by atrial pacing or A V refractory period measurements Furthermore a significant disparity between the effects of procaine amide on antero grade and retrograde bypass refractoriness was observed

Tachycardias could be induced in nine of the 13 patients with a mean rate of 167 2 ± 7 9 beats per minute delta waves were absent during all episodes of tachycardia Procaine amide prevented tachycardia induction in six of the nine patients

Procaine amide therefore demonstrates electrophysiologic effects which would be beneficial for prevention or treatment of reciprocating tachycardias in the WPW syndrome Moreover procaine amide would be an ideal agent for the prevention of rapid ventricular rates in patients with the WPW syndrome and atrial fibrillation

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Electrophysiologic effects of tolamolol on atrioventricular conduction in man

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Tolamolol is a beta adrenergic blocking agent with the following chemical designation 4 [2 (hydroxy 3 O toloyloxy propylamino) ethoxy] benzamide hydrochloride The drug is an effective antagonist of isoproterenol induced tachycardia and has been shown to be equipotent to propranolol and fifty times more potent than proctolol in antagonizing exercise induced tachycardia in animals [2] Like proctolol tolamolol has been shown to possess considerable selectivity for cardiac tissue in experimental animals and in man In experiments on papillary muscle and guinea pig atria tolamolol demonstrated considerably less cardiac depressant activity than equivalent doses of propranolol [2] Although preliminary hemodynamic studies in man have demonstrated some negative inotropic effect with intravenous tolamolol [3] controlled comparisons with equivalent doses of propranolo have not been carried out in man

Recent work has suggested that tolamolol may be as effective as propranolol in the treatment of angina pectoris [4] and in addition is effective in the treatment of a variety of supraventricular tachyarrhythmias and certain digitalis induced arrhythmias [5,1]

The purpose of this study was to evaluate the effects of tolamolol on the electrophysiologic properties of the S A node A V node and His Purkinje system in man by means of intracardiac electrograms and the extrastimulus method

Materials and methods

Thirteen patients underwent right heart catheterization in the nonsedated postabsorptive state after informed consent had been obtained They were studied for known or suspected disorders of cardiac rhythm or conduction All patients were in sinus rhythm and no patient had received cardioactive medication for at least 1 week prior to the time of catheterization

With the use of local anesthesia a quadripolar catheter was percutaneously introduced into an antecubital vein and under fluorscopic guidance positioned against the lateral wall of the high right atrium The distal two electrodes were used for atrial pacing and the proximal two electrodes for recording a high right atrial electrogram A tripolar catheter was percutaneously introduced into the femoral vein and positioned across the tricuspid value to record electrical activity from the bundle of His as previously described [1] A bipolar pacing catheter was percutaneously introduced into another arm vein and positioned at the right ventricular apex for ventricular stimulation Atrial pacing was performed with a programmed digital stimulator which delivered rectangular impulses of 1 5 msec duration at twice diastolic threshold Ventricular pacing was carried out in a similar manner with the lowest milliamperage that permitted reliable ventricular capture Studies of the refractory period were performed by the extrastimulus method [13] Studies of sinus node suppression

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were carried out by pacing the right atrium for 1 minute at each of 4 fixed cycle lengths (600, 550, 500, and 460 msec.)[14] Sinus node escape time was then measured (see definition of terms) after cessation of pacing at each cycle length. Intracardiac electrograms, standard ECG Leads I, II, III, and V_1, and time lines generated at intervals of 10 and 100 msec. were simultaneously displayed on a multichannel oscilloscope and recorded on magnetic tape. Recordings were subsequently reproduced on photographic paper at a speed of 150 mm. per second. Care was taken to insure adequate grounding of all equipment.

After completion of control studies, tolamolol was infused intravenously at a rate of 4 mg. per minute, with the total dose ranging from 4 to 30 mg. (mean, 17 mg. or 0.24 mg./Kg.). Because of the experimental nature of the drug, incremental doses were administered to the 13 patients studied. Repeat electrophysiologic studies were initiated 5 minutes after infusion of the drug and completed within 45 minutes. Five patients subsequently received a small dose (0.5 or 1.0 mg.) of intravenous atropine 45 minutes after receiving tolamolol. Repeat electrophysiologic studies were initiated 2 minutes after the administration of atropine and completed within 20 minutes. Heart rate and supine blood pressures were carefully monitored throughout each study. Results were analyzed by means of the Student's t test for paired data.

In addition, a separate group of 5 patients was studied in the supine resting position in order to evaluate the effects of incremental doses of tolamolol on sinus rate. Three subjects had mild hypertension controlled with diuretics and 2 had arteriosclerotic heart disease. All cardioactive medications were discontinued at least 1 week prior to the time of study, and none of the patients had evidence of congestive heart failure, atrial arrhythmias, or sinus node dysfunction. A slow intravenous drip of 5 per cent dextrose in water was started in each patient, and a 30 minute control period was observed. Tolamolol was then administered intravenously as a 2 mg. bolus every 10 minutes up to a total dose of 20 mg. Heart rate was monitored by standard ECG (Lead II) recorded at 5 minute intervals during the control period and at intervals of 1, 5, and 10 minutes after each 2 mg. bolus of tolamolol. Blood pressure was simultaneously monitored with a sphygmomanometer. Control sinus cycle length was calculated as the average of 20 consecutive sinus beats recorded 1 minute prior to the administration of tolamolol. Sinus cycle length for each incremental dose of tolamolol was calculated as the average of 20 consecutive sinus beats recorded 5 minutes after each 2 mg. injection.

Definition of terms

S_1, A_1, H_1, V_1 represent the stimulus artifact, atrial electrogram, His bundle electrogram, and ventricular electrogram of the basic drive beat.

S_2, A_2, H_2, V_2 represent the stimulus artifact, atrial electrogram, His bundle electrogram, and ventricular electrogram of the premature beat.

A-V nodal conduction time is approximated by the A-H interval, which is measured from the onset of the low right atrial electrogram to the onset of the His bundle deflection (normal values for this laboratory, 60 to 140 msec.).

His-Purkinje conduction time is approximated by the H-V interval, which is measured from the onset of the His bundle deflection to the onset of ventricular activation (normal values for this laboratory, 30 to 55 msec.).

Sinus escape time (SET) is defined as the interval between the last paced atrial beat and the first sinus escape beat as verified by P wave morphology and a high to low atrial activation sequence and was measured from the high right atrial electrogram recordings.

Effective refractory period (ERP) of the atrium is defined as the longest S_1S_2 interval at which S_2 fails to depolarize the atrium.

Effective refractory period of the A-V node is defined as the longest A_1A_2 interval at which A_2 fails to depolarize the His bundle.

Functional refractory period (FRP) of the A-V node is defined as the shortest H_1H_2 interval that results from any A_1A_2 provided that A-V conduction is not limited by atrial refractoriness.

ERP of the His-Purkinje system (HPS) is defined as the longest H_1H_2 interval at which H_2 fails to conduct to the ventricles.

Relative refractory period (RRP) of the HPS is the longest H_1H_2 at which H_2 conducts to the ventricles with a longer H-V interval than that of the basic drive beat or with a QRS of aberrant configuration. The limitations of this definition have been discussed previously.[15,16]

ERP of the ventricle is defined as the longest

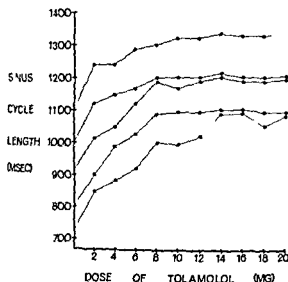


Fig 1 The effect of incremental doses of tolamolol on sinus rate (5 patients) Sinus cycle length (msec) is plotted as a function of the cumulative dose of tolamolol administered Little or no additional prolongation of sinus cycle length occurred as the total dose exceeded 10 mg intravenously

S_1S_2 interval at which S_2 fails to depolarize the ventricle during ventricular stimulation

Ventriculo atrial (V A) conduction time is defined as the interval from the stimulus artifact to the onset of the low right atrial electrogram as observed during right ventricular pacing In these patients latency between the stimulus artifact and the onset of ventricular activation as seen on standard ECG was not observed Criteria for retrograde conduction and activation of the atria have been described previously

Retrograde ERP of the A V node is defined as the longest S H_2 interval at which the retrograde His bundle deflection of the premature beat (H_2) is not followed by retrograde atrial depolarization Because the retrograde His bundle deflection of the basic drive beat (H_1) is usually obscured by the ventricular electrogram (V_1) and because the S H_1 interval usually remains constant [7] S H_2 may be used in place of the H H_2 interval in retrograde studies in man

Results

Dose response studies (Fig 1) Maximal prolongation of sinus cycle length (SCL) by tolamolol occurred after a total dose of 8 mg in 3 of 5 patients 10 mg in 1 patient and 14 mg in 1 patient Subsequent 2 mg increments of tolamolol up to a total dose of 20 mg produced little or no additional sinus slowing in these patients (Fig 1) The effect of each 2 mg increment on sinus rate was maximal within 5 minutes after infusion of the drug In all patients nearly maximal prolongation of sinus cycle length (> 75 per cent of peak SCL) persisted for at least 90 minutes and significant sinus slowing (> 50 per cent of peak SCL) persisted for at least 3 hours after a total dose of 20 mg of tolamolol No significant changes in supine blood pressure were observed Two patients experienced transient postural hypotension after completion of the study

All subsequent results pertain to the group of 13 patients studied with intracardiac electrograms The essential clinical data for this group are presented in Table I

Table I Clinical data and drugs administered

Patient No	Age	Sex	Diagnosis (ECG)	Tolamolol mg (mg/kg)	Atropine (mg)
1	75	M	ASHD (VPBs)	4 (0 07)	0
2	62	M	ASHD (LBBB VPBs)	8 (0 08)	0
3	61	M	ASHD (VPBs)	12 (0 15)	0
4	6?	M	ASHD (RBBB/LAD and 1 AVB)	8 (0 11)	0 5
5	59	M	ASHD (LBBB)	12 (0 16)	0
6	67	M	ASHD (ASMI VPBs)	16 (0 23)	1
7	56	M	HHD (LVH)	20 (0 21)	1
8	56	F	NHD (RBBB)	30 (0 45)	0
9	69	M	ASHD (DMI VPBs)	20 (0 27)	1
10	56	M	WPW A	20 (0 28)	0
11	58	M	Mitral prolapse (VPBs)	30 (0 53)	1
12	24	F	Mitral prolapse (STTW Ab)	16 (0 27)	0
13	25	M	NHD (Normal)	25 (0 34)	0

Numbers do not designate the temporal sequence in which patients were studied.

Abbreviations ASHD = arteriosclerotic heart disease HHD = hypertensive heart disease NHD = no heart disease LBBB = left bundle branch block RBBB = right bundle branch block LAD = left axis deviation 1 AVB = first-degree A V block WPW A = Wolff Parkinson White syndrome-type A VPBs = ventricular premature beats ASMI = anteroseptal myocardial infarction DMI = diaphragmatic myocardial infarction LVH = left ventricular hypertrophy STTW Ab = S-T and T wave abnormalities.

Sinus node function (Table II)

Sinus cycle length (SCL) Administration of

Table II Antegrade conduction studies and sinus escape times before and after tolamolol (msec)

Patient No	Sinus cycle length		A H interval		H V interval		Sinus escape time		PCL at onset of Wenckebach	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	595	680	85	100	40	40	770	980	310	3[illegible]0
2	700	840	105	110	75	75	1 074	1 287	330	460
3	670	685	100	115	40	40	1 100	1 187	370	460
4	1 050	1 060	210	230	60	60	1 205	1 290	750	850
5	630	1 000	60	70	70	70	1 193	1 203		*
6	900	990	80	90	55	55	1 120	1 124	430	460
7	800	8[illegible]0	115	130	50	50	9[illegible]4	1 034	300	500
8	760	780	90	100	45	45	1 170	1 170	460	460
9	760	820	90	120	55	55	1 004	1 280	370	500
10	830	850	90	90	†	†	947	1 090		
11	960	1 140	90	100	45	45	1 184	1 277	370	460
12	560	700	90	100	50	50	854	944	300	400
13	670	740	70	90	40	40	760	1 000	330	430
Mean	752 ± 43	856 ± 41	98 ± 10	111 ± 10	52	52	1 025 ± 43	1 143 ± 34	392 ± 38	486 ± 38
P value	P < 0 01		P < 0 001				P < 0 001		P < 0 001	

*Wenckebach block not observed during atrial pacing
†His bundle deflection preceded by onset of ventricular activation (WPW)
PCL = paced cycle length

Table III Refractory period data before and after tolamolol (msec)

Patient No	ERP of atrium		ERP of A V node		FRP of A V node		ERP of ventricle	
	Before	After	Before	After	Before	After	Before	After
1	260	250	†	320	330	380		
2	245	26[illegible]	280	350	39[illegible]	468		
3	285	255	330	380	485	518		
4	320	280	600	620	770	810		
5	260	275	†	†	†	†	300	280
6	290	280	365	430	453	500	220	240
7	300	260	375	395	515	553		
8	300	295	385	420	463	483	2[illegible]0	230
9	240	240	29[illegible]	420	430	575		
10	‡	‡	‡	‡	‡	‡		
11	285	2[illegible]0	350	435	430	510		
12	210	210	220	260	3[illegible]3	433		
13	250	270	260	340	370	440		
Mean	270 ± 9	263 ± 6	346 ± 32	405 ± 29	455 ± 35	515 ± 33	256 ± 23	250 ± 15
P value	P > 0 1		P < 0 001		P < 0 001		P > 0 1	

Each value represents an average of results obtained at multiple comparable cycle lengths (see Results)
†Electrophysiologic studies limited by atrial refractoriness
‡Electrophysiologic studies limited by induction of atrial fibrillation during atrial vulnerable period

tolamolol resulted in prolongation of SCL in all patients (mean + 104 msec, $p < 0\ 01$) This corresponds to a 14 per cent increase in SCL or a mean decrease in heart rate of 10 beats per minute The effects of tolamolol on SCL are presented in Table II

Sinus escape time (SET) Administration of tolamolol resulted in prolongation of SET in 11 of 13 patients and no change in 2 patients (mean + 118 msec $p < 0\ 001$) Sinus escape times presented in Tables II and IV represent an average of values determined at 4 comparable cycle lengths (460 500 550 and 600 msec) for each patient When average escape times were

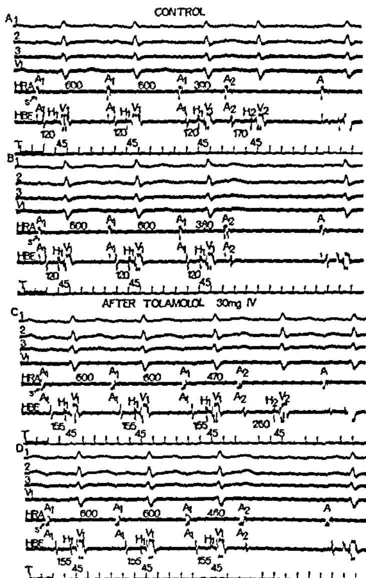


Fig 2 Effect of tolamolol on effective refractory period of the A-V node (Patient No 11) In all panels the basic atrial cycle length is constant at 600 msec In *panel A* (control) an atrial premature depolarization (A) coupled to basic drive beat (A) at an interval of 390 msec is conducted with an A H interval of 170 msec In *panel B* the A A coupling interval is reduced to 380 msec and the premature depolarization (A) is blocked in the A-V node This is the longest A A interval (380 msec) at which A fails to propagate to the HPS thus defining the effective refractory period (ERP) of the A-V node during the control period. In *panel C* (after tolamolol 30 mg intravenously) an atrial premature depolarization (A) coupled to the basic drive (A) at an A A interval of 470 msec is conducted with an A H interval of 260 msec In *panel D* the A A coupling interval is reduced to 460 msec and the premature depolarization (A) is blocked in the A V node thus defining the ERP of this tissue after tolamolol. When panels *B* and *D* are compared it is apparent that tolamolol has prolonged the ERP of the A-V nod by 80 msec The presence of a drug effect is further substantiated by an increase in A-V nodal conduction time during the basic drive beats (A H) from 120 msec during control studies (*panels A* and *B*) to 155 msec after tolamolol (*panels C* and *D*)

Table IV Effects of atropine on tolamolol induced changes in antegrade conduction (msec)

Patient No	Sinus cycle length			A H interval			H V interval			Sinus escape time			Paced CL at onset of Wenckebach		
	C	T	A	C	T	A	C	T	A	C	T	A	C	T	A
4	1 0_0	1 060	960	210	230	220	60	60	60		*	*	750	850	750
6	900	990	680	80	90	90	55	55	55	*	*	*	430	460	400
7	800	8_0	700	115	130	95	50	50	50	954	1 034	830	300	500	310
9	760	820	620	90	120	100	55	55	55	1 004	1,280	1 034	3_0	500	4_0
11	960	1 140	860	90	100	80	45	45	45	1 184	1 277	1 155	370	460	430
Mean	894 ± 52	972 ± 60	804 ± 60	117 ± 24	134 ± 25	117 ± 25	53	53	53	1 047 ± 70	1 197 ± 81	1 006 ± 94	444 ± 79	5_4 ± 74	462 ± 75
P value		P < 0 0_			P < 0 05						P < 0 005			P < 0 05	

Sinus escape times not studied after atropine
P values compare post atropine with post tolamolol values only
Abbreviations C = control T = tolamolol A = atropine CL = cycle length

compared with results determined at any single cycle length no significant difference in the magnitude of change was observed and the statistical significance achieved by these changes was the same

Antegrade conduction (Table II)

A V node Administration of tolamolol resulted in a statistically *significant increase in A V nodal* conduction time during sinus rhythm in 12 of 13 patients (mean + 13 msec, $p < 0.001$) In 1 patient with WPW-type A pre excitation there was no change in A H interval after tolamolol Onset of A-V nodal Wenckebach block during atrial pacing occurred at longer paced cycle lengths in 10 of 11 patients and was unchanged in 1 patient (mean + 94 msec $p < 0.001$) In 2 patients, Wenckebach block did *not occur* with rapid atrial pacing before or after tolamolol

His Purkinje system (HPS) Conduction time within the HPS remained unchanged *in all* patients after tolamolol both during sinus rhythm and during rapid atrial pacing Tolamolol had no effect on HPS conduction time in 3 patients who demonstrated prolonged H V intervals during control studies (Table II)

Refractory period studies (Table III) Refractory period data presented in Tables III and V represent values which were averaged from results obtained at multiple comparable cycle lengths (range, 600 to 900 msec) for each patient In view of the known effect of cycle length on refractory periods[19] these data were compared with refractory period data determined at a single cycle length (600 msec) before and after tolamolol in 8 patients There were no significant differences in the magnitude of the changes observed and no differences in the degree of statistical significance achieved by these changes when averaged data were compared with results obtained at a single cycle length in this group of patients

Atrium Tolamolol exerted variable and statistically insignificant effects on the effective refractory period (ERP) of the atrium This parameter was shortened in 7 patients prolonged in 3 patients, and unchanged in 2 patients (mean−13 msec $p > 0.1$)

A V node Tolamolol prolonged the effective refractory period of the A V node in 10 of 10 patients in whom this parameter could be measured (mean + 59 msec $p < 0.001$) Fig 2 illustrates prolongation of the ERP of the A V node after tolamolol Tolamolol significantly prolonged the functional refractory period (FRP) of the A V node in 11 of 11 patients (mean + 60 msec $p < 0.001$)

His Purkinje system During control studies the relative refractory period (RRP) of the HPS was reached in 4 patients and the ERP of the HPS was reached in 1 patient Because of the delay in A V nodal conduction time and the marked increase in A V nodal refractoriness induced by tolamolol, comparable H_1H intervals could not be attained in any patient after the drug The effects of tolamolol on the A V node thus prevented assessment of any possible effects

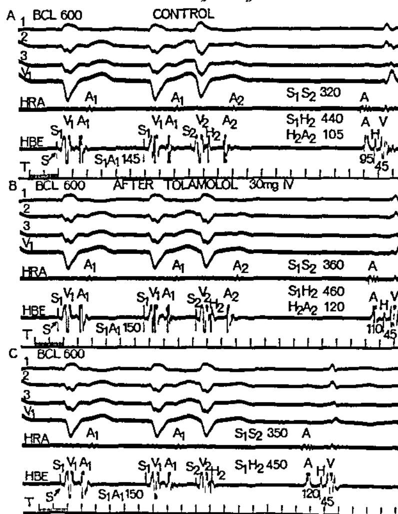


Fig 3 Effect of tolamolol on retrograde A V nodal conduction and refractoriness (Patient No 8) *Panel A* demonstrates control and *panels B* and *C* demonstrate post tolamolol retrograde refractory period studies The right ventricle is paced at a basic cycle length (S S) of 600 msec and premature ventricular beats (S) are coupled to every eighth drive beat The longest S H interval which fails to depolarize the atrium defines the retrograde ERP of the A V node (see definitions) In *panel A* (control) a premature beat (S) is delivered at a coupling interval of 3 0 msec resulting in an S H interval of 440 msec and a retrograde A V nodal conduction time (H A) of 10ɔ msec During control studies progressively early premature ventricular beats continued to conduct retrogradely to the atria and the retrograde ERP of the A V node was not encountered In *panel B* (after tolamolol) an S delivered at a coupling interval of 360 msec results in an S H interval of 460 msec thus arriving at the A V node 20 msec later than the S displayed in panel *A* Despite its later arrival and because of the effects of tolamolol, the premature beat in *panel B* encounters a longer retrograde A V nodal conduction time (H A = 1?0 msec) than the premature beat in *panel A* Comparison of *panels A* and *B* thus con?irms prolongation of retrograde A V nodal conduct on time by tolamolol in this patient In *panel C* (after tolamolol) an S introduced at a coupling interval of 350 msec results in an S H interval of 450 msec which fails to depolarize the atria (i e is blocked in the A V node) thus defining the retrograde ERP of the A V node During control studies the shortest S H interval observed prior to encountering the ERP of the ventricle was 415 msec and conduction to the atria was observed Tolamolol ther fore prolonged the retrograde ERP of the A V node by more than 35 msec in this patient but the precise magnitude of prolongation could not be determined because of failure to reach the retrograde ERP of the A V node during control studies.

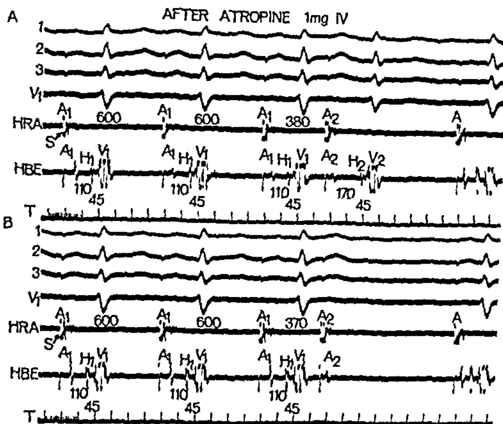


Fig 4 Effect of atropine on the ERP of the A V node (Patient No 11) This patient received atropine (1 0 mg intravenously) immediately after completion of electrophysiologic studies with tolamolol (30 mg intravenously) The ERP of the A V node was prolonged from 380 msec during control studies to 460 msec after tolamolol (see Fig 2) At the same basic atrial cycle length (600 msec) after atropine an atrial premature depolarization A introduced at a coupling interval (A A) of 380 msec conducts with an A H interval of 170 msec (*panel A*) In *panel B* the A A coupling interval is reduced to 370 msec and A is blocked in the A V node thus defining the ERP of this tissue after atropine When compared with the ERP of the A V node after tolamolol (460 msec) as *shown in Fig 2 (panel D) it is apparent that atropine has shortened the FRP of the A V node by 90 msec* The presence of a drug (atropine) effect is further substantiated by a decrease in A V nodal conduction time during the basic drive beats A H, from 155 msec after tolamolol (*Fig 2 panels C* and *D*) to 110 msec after atropine (*panels A* and *B* above)

on the relative or effective refractory periods of the HPS

Retrograde studies

Ventriculo atrial (V A) conduction time Retrograde conduction studies were performed in 5 patients In 2 patients (Nos 1 and 5) V A conduction time at comparable paced ventricular rates did not change after tolamolol and retrograde A V nodal Wenckebach block did not occur before or after the drug in either patient In 2 patients (Nos 4 and 8), V A conduction time was prolonged at comparable paced rates (mean + 10 msec), and retrograde A V nodal Wenckebach block occurred at longer paced cycle lengths after tolamolol (mean + 180 msec) Because of the few patients involved, these changes did not achieve statistical significance In 1 patient (No 13) consistent V A conduction was observed during control studies, whereas after tolamolol V A dissociation was observed at all ventricular paced rates in spite of concomitant sinus deceleration

Retrograde ERP of the A V node Tolamolol caused insignificant prolongation (+ 10 msec) of the retrograde ERP of the A V node in 1 patient (No 5) in whom this parameter could be determined at a comparable cycle length before and after the drug In a second patient (No 8) the retrograde ERP of the A V node was not reached during control studies because this parameter was exceeded by the ERP of the ventricle After tolamolol the retrograde ERP of the A V node was significantly prolonged and was, therefore encountered *prior* to the ERP of the ventricle Fig 3 illustrates prolongation of V A conduction time and prolongation of the retrograde ERP of the A V node in this patient In 2 additional

Table V Effects of atropine on tolamolol induced changes in refractory periods (msec)

Patient No	ERP of atrium			ERP of A V node			FRP of A V node		
	C	T	A	C	T	A	C	T	A
4	320	280	300	600	620	550	770	810	770
6	290	280	260	365	430	340	453	500	430
7	300	260	270	375	395	<270	515	553	400
9	240	240	240	295	420	335	430	575	448
11	285	270	260	350	435	370	430	510	445
Mean	287 ± 13	266 ± 7	266 ± 9	397 ± 52	460 ± 40	373 ± 47	519 ± 64	589 ± 56	498 ± 68
P value		P > 0 1			P < 0 005			P < 0 025	

Each val represents an average of result obtained at m lt pl compa bl cycle lengths (see Results)
P alues compare post atropin with post tol molol val es only
Abbreviations C = control T = tolamolol A = atropine

patients in whom control studies on the retro grade refractory period were performed compa rable data could not be obtained after tolamolol In one of these patients retrograde A V nodal Wenckebach block occurred at the basic drive cycle length (900 msec) and in the other patient complete V A dissociation occurred at all paced cycle lengths after tolamolol thus precluding assessment of the retrograde ERP of the A V node

ERP of the ventricle Tolamolol did not signif icantly alter the ERP of the ventricle in 3 of 3 patients (mean – 6 msec p > 0 1)

A small decrease in calculated mean blood pressure in the supine position was observed in 6 of 13 patients after tolamolol and no change was seen in 7 of 13 patients (mean – 3 mm Hg p < 0 025) No untoward side effects were observed

Electrophysiologic studies after atropine (Tables IV and V) The following changes were observed in 5 patients who received atropine (0 5 or 1 0 mg intravenously) immediately upon completion of electrophysiologic studies with tolamolol (data compare post atropine with post tolamolol values for each parameter) (1) sinus cycle length shortened significantly in 4 of 5 patients (mean – 168 msec p < 0 05) (2) sinus escape time shortened significantly in 3 of 3 patients (mean – 191 msec p < 0 05) (3) A V nodal conduction time during sinus rhythm decreased significantly in 4 of 5 patients (mean – 17 msec p < 0 05) (4) HPS conduction time was unchanged in 5 of 5 patients (5) the ERP of the atrium was not significantly altered in 5 of 5 patients (6) the ERP and FRP of the A V node shortened significantly in 5 of 5 patients (mean – 87 and – 91 msec respectively p < 0 05) Fig 4 illustrates the effect of atropine in shortening the ERP of the A V node after this parameter was prolonged by tolamolol (see Fig 2)

Discussion

In this study tolamolol administered to 13 patients in a dose range of 4 to 30 mg intrave nously significantly prolonged spontaneous sinus cycle length sinus escape time A V nodal conduction time and the effective and functional refractory periods of the A V node Tolamolol did not affect His Purkinje conduction time in any patient including 3 subjects who manifested prolonged H V intervals during control studies (Table II) This latter observation is consistent with the findings in most previous reports in which it has been shown that conduction in the HPS is insensitive to adrenergic stimulation or blockade [9 6] In addition no consistent or signifi cant effects on atrial and ventricular refractori ness were observed Because of the increase in A V nodal conduction time and refractoriness in duced by tolamolol the HPS was in a sense protected by the drug Thus conduction delay or block within the A V node consistently precluded assessment of the relative and effective refractory periods of the HPS by preventing attainment of critically short $H_1 H_2$ intervals after tolamolol A similar situation existed in previous studies with propranolol and digoxin

The findings in this study are in close agree ment with preliminary observations in open chest dogs which demonstrated a 20 per cent increase in

the P R interval and a 10 per cent increase in the FRP of the A V node after tolamolol (0 3 to 0 4 mg /Kg intravenously)[28] In addition, the study reported no effect on conduction or excitability within the HPS, and a tenfold or greater increase in ventricular fibrillation threshold after tolamolol [8]

The electrophysiologic effects observed after the administration of tolamolol were qualitatively identical to those previously observed with propranolol in this laboratory [24] The fact that the drugs were evaluated in different patient populations precludes any valid comparison with regard to relative potency of the two agents in altering various properties of the cardiac conduction system No consistent relationship between the effects of tolamolol on antegrade and retrograde conduction was observed in this study Propranolol has been reported to have a greater effect on retrograde than on antegrade A-V nodal conduction and refractoriness in dogs [29] In this study, complete V A block without antegrade block was observed in 1 patient (No 13) after tolamolol, whereas consistent V A conduction was present at all ventricular paced rates during control studies A similar phenomenon after propranolol has been reported in man [30]

The effect of incremental doses of tolamolol on sinus cycle length reached a peak at or near a dose of 10 mg in the 5 patients studied At higher doses little or no additional depression of resting sinus rate was observed No statement can be made, however, with regard to the possible effect of larger doses of tolamolol on ambulatory heart rate or exercise induced tachycardia There appeared to be a trend in both groups of patients toward greater degrees of sinus slowing in subjects with faster resting sinus rates regardless of the dose of tolamolol administered This may reflect a relationship between the degree of sympathetic tone and the magnitude of sinus depression produced by tolamolol Further studies are necessary to properly assess the significance of this relationship

Atropine (0 5 or 1 0 mg intravenously) reversed the effects of tolamolol on the sinoatrial node and A V conducting system The observed effects of atropine on automaticity, conduction and refractoriness have been described previously[31-34] and are thought to result primarily from parasympatholytic activity in this dose range[11] The possibility that tolamolol possesses vagomimetic as well as beta adrenergic blocking properties can not be excluded However, it seems more likely that the electrophysiologic effects of tolamolol and atropine are dissociated and result from distinct action on separate parts of the autonomic nervous system The changes observed after atropine in this study are consistent with the elimination of a normal degree of resting vagal tone by the drug These observations suggest that atropine could serve as an effective alternative to isoproterenol in reversing the effects of tolamolol on the electrophysiologic properties of the sinus and A-V nodes

None of the patients in this study was receiving digitalis at the time of catheterization We have subsequently used tolamolol (10 mg intravenously) in 2 patients with atrial fibrillation in whom the ventricular response was inadequately controlled with digoxin alone The combination of tolamolol and digoxin produced effective slowing of the ventricular response in both patients

In conclusion tolamolol is a potent beta adrenergic blocking agent which produces moderate depression of sinus node automaticity and significant prolongation of A V nodal conduction time and refractoriness These latter properties explain the efficacy of the drug in controlling the ventricular response in patients with atrial flutter or fibrillation, and in the termination of A V nodal reentrant supraventricular tachycardias[9,10] The lack of effect on HPS conduction time renders the drug safe in patients with infra-His bundle conduction disturbances

Summary

The electrophysiologic effects of tolamolol (UK 6558 01) a beta adrenergic blocking agent, were studied in 13 patients by means of intracardiac electrograms and the extrastimulus method Tolamolol (4 to 30 mg intravenously) resulted in (1) prolongation of sinus cycle length (SCL) in all patients ($p < 0.01$) (2) prolongation of sinus escape time (SET) in 11 of 13 patients ($p < 0.001$) (3) prolongation of A V nodal conduction time during sinus rhythm in 12 of 13 patients ($p < 0.001$) (4) onset of A V nodal Wenckebach block at longer paced cycle lengths in 10 of 11 patients ($p < 0.001$), (5) prolongation of the functional refractory period (FRP) of the

A V node in 11 of 11 patients ($p < 0.001$) and (6) prolongation of the effective refractory period (ERP) of the A V node in 10 of 10 patients ($P < 0.001$) Tolamolol had no effect on His Purkinje system (HPS) conduction time in any patient including 3 patients with abnormal H V intervals Because of the marked increase in A V nodal conduction time encountered by premature atrial depolarizations the relative and effective refractory periods of the HPS could not be determined in any patient after tolamolol Atropine (0.5 or 1.0 mg intravenously) significantly reversed the effects of tolamolol on sinus cycle length (4 of 5 patients) sinus escape time (3 of 3 patients) A V nodal conduction time (4 of 5 patients) and A V nodal refractoriness (5 of 5 patients)

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Case reports

Idiopathic cardiomyopathy and skeletal muscle abnormality

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Idiopathic cardiomyopathy is the term used to describe dysfunction or disease of the myocardium of unknown cause The term idiopathic cardiomyopathy used in this way is a blanket term for a host of diverse diseases Predisposing causes such as alcoholism and known viral infections have been excluded Cases discussed under this heading also exclude those cases with primary muscular disorder such as Duchenne s or Becker s dystrophy or myotonia dystrophica where the heart muscle is known to be involved Idiopathic cardiomyopathy is subdivided into congestive obliterative and hypertrophic varieties by Goodwin[1] the first is associated with dilation and contractile failure the second group shows evidence of endomyocardial fibrosis and the third group shows evidence of obstruction to blood flow

Comments on skeletal muscle involvement in idiopathic cardiomyopathy date back to Evans in 1949 but the first detailed pathologic study of skeletal muscle in idiopathic cardiomyopathy was carried out by Shafiq and co workers

Three cases are presented in this paper

Case reports and investigations

Case 1 A 26-year-old male gave a history of slowly progressive muscular fatigability and weakness since the age of [illegible] years. He went into the army at the age of 18 and at this stage found it extremely difficult to keep up with his duties and on one occasion was subjected to a particularly arduous period of physical work

This resulted in hospitalization when he was found to be in cardiac failure and a diagnosis of idiopathic congestive cardiomyopathy was made After prolonged bed rest he recovered from this period of cardiac decompensation completed his studies at the University married and has managed to live a reasonably active life within the limits of his physical and cardiac disability There was no history of any other serious illness or of any neuromuscular disease in the family He had not received medication of any kind for the last few years

Examination revealed an adult male of average build There was moderate generalized muscle weakness most noticeable in the more proximal muscles The tendon reflexes were present and equal but depressed. The rest of the physical examination apart from the heart, was normal. Full routine blood and metabolic studies were normal Lactic acid estimations were carried out on venous blood from the forearm following one minute of ischemic exercise The resting lactic acid level was slightly elevated rose normally after exercise but remained consistently higher than normal for more than seven minutes indicating either excessive lactic acid production or a slow circulatory time As there was no evidence of any cardiac decompensation at the time of the test the former explanation is favored Enzyme studies revealed an elevated creatine phosphokinase (CPK) of 80 units (normal 0 to 50 units)

Electromyographic study of muscle using concentric needle electrodes revealed evidence of a diffuse myopathy Many of the motor units were of low voltage and abnormally polyphasic There was no evidence of denervation activity

Nerve conduction studies were carried out for both motor and sensory modalities on the median and ulnar nerves and these were found to be within normal limits

Muscle was removed from the posterior third of the left deltoid muscle under local anesthetic and cryostat sections were processed for histologic and histochemical analysis On the NAD diaphorase and succinic dehydrogenase stains in particular there was evidence of subsarcolemmal accumulations which were presumed to be mitochondria (Figs. 1 and 2) The abnormality was for the most part confined to the Type I fibers (classification of Dubowitz and Pearse)

Muscle for electron microscopic study was preserved initially in gluteraldehyde and subsequently embedded in eraldite Ultramicroscopic study revealed excessive accumulations of mitochondria The mitochondria showed marked variation in size and shape and many showed the presence of paracrystalline inclusions in various stages of growth The inclusions varied considerably in size with the large particles taking up long parallel circular or car park appearances Some of the inclusion bodies were noted to have burst out of

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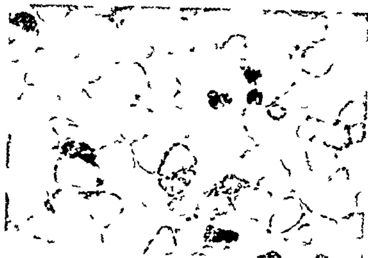


Fig 1 An NAD diaphorase preparation showing involvement of the Type 1 fibers There are dense accumulations of mitochondria in the involved cells particularly in the subsarcolemmal site ×80



Fig 2 An NAD diaphorase showing involvement of the Type 1 fibers with subsarcolemmal collections of mitochondria ×320

the original site in the mitochondria and have obviously continued to grow in the sarcoplasm (Figs 3 4 and 5)

Case 2 R C aged 13 presented initially to the cardiologists at the age of 11 years with a complaint of dyspnea and tachycardia A diagnosis of idiopathic congestive cardiomyopathy was made He also complained of generalized muscular weakness and was referred for further study He gave a long history of progressive muscular weakness over many years He tended to fall excessively and had difficulty in lifting heavy objects There was no history of any nerve or muscle disease in the family He has three brothers who are apparently in good health

Examination revealed a young teenager who walked with a waddling gait which in addition tended to be high stepping because of weakness of dorsiflexion at the ankle joints

Physical examination revealed evidence of generalized muscular weakness affecting especially the extensors of the ankle joints The proximal muscles acting about the hip joint were also involved and his shoulder girdle muscles were involved to a lesser degree The tendon reflexes were universally absent There was an obvious degree of jerkiness about his movements particularly noticeable with the hands when assembling wooden blocks

Electromyography revealed a mixture of normal motor units and excessively high voltage units while others were of shorter duration and of lower voltage than normal There was no evidence of fibrillation activity but fasciculation activity was found in several muscles Nerve conduction studies carried out on both upper and lower extremities for both sensory and motor function fell within the normal range

Full blood studies and metabolic studies were within normal limits The CPK was 46 6 units

Muscle biopsy from the right biceps was carried out and this was subjected to histologic and histochemical analysis as well as ultramicroscopic study There was evidence of marked grouping of individual fiber types and of grouped atrophy The electron microscopic study confirmed the presence of myofibrillar loss and distortion and destruction of the Z lines characteristic of denervation there was also excessive folding of the plasma membrane (Fig 6) The nerve terminal and end plate study revealed that the terminal innervation ratio was increased to 1 4 (normal 1 25)[3] There was evidence of new sprouting of ultraterminal branching and of multiple innervation of single muscle fibers There were also marked variations in size and shape of the end plates (Fig 7)

Case 3 C G aged 26 presented to the Johannesburg General Hospital complaining of shortness of breath A diagnosis of congestive cardiac failure was made Full cardiologic study concluded that the cardiac lesion was one of idiopathic congestive cardiomyopathy which was accompanied by atrial fibrillation The patient gave an additional history of weakness of the legs which he first noticed while playing football about five years earlier and stated that his legs seemed to buckle under him There was no family history of muscle disease Examination revealed that motor power was generally decreased in the shoulder girdle muscles and the upper extremity reflexes were absent while the lower limb reflexes were just obtainable There was also some weakness of muscles acting about the pelvic girdle Blood and metabolic studies were normal apart from an elevated sedimentation rate of 30 mm Hg in one hour a CPK of 65 units and aldolase of 47 units (normal range 5 to 31 units)

Electromyography revealed an increase of low voltage short duration polyphasic activity in the proximal muscles of both upper and lower extremities There was no evidence of denervation activity

Nerve conduction studies both motor and sensory were normal The myoneural junction responded normally to repeated trains of stimuli

A muscle biopsy was taken from the left deltoid for histology histochemistry nerve terminal end plate and electron microscopic study Many of the fibers were found to contain vacuoles (Fig 8) This was particularly well seen in the phosphorylase preparation (Fig 9) There was an increased number of internal nuclei and areas of small groups of cells showing degeneration In other areas regeneration was obvious as evidenced by small cells with large nuclei and basophilic cytoplasm A nerve terminal and endplate study revealed large numbers of small endplates with poor development The ultramicroscopic examination of muscle revealed areas within the muscle which were depleted of myofibrils with streaming and destruction of the Z-lines (Figs 10 and 11)



Fig 3 Fine structure of muscle revealing collections of mitochondria many of which show paracrystalline inclusion bodies. There is marked variation in size and shape of the mitochondria many are swollen and show loss of cristae There is also evidence of loss of myofibrils ×18 000

Discussion

The hypertrophic form of cardiomyopathy has emerged as a clear cut clinical syndrome the hemodynamics of which are quite characteristic In this variety there occurs a generalized hyper trophy particularly of the left ventricle which may be so marked as to functionally cause a subaortic stenosis Hootsmans and Meerschwan[7] reported on a skeletal muscle study of 23 patients suffering from hypertrophic obstructive cardio myopathy The investigation was mainly electro diagnostic though enzyme estimations were re corded and in four cases the CPK was marginally elevated Fifteen of the 23 patients investigated gave electromyographic evidence of a generalized myopathy In three of their cases histochemical and histologic studies were performed and these were reported to be normal however no details of the histochemical study were published and this statement conflicts with the presence of abnor mal electromyographic findings and also with the histochemical finding of Shafiq and co workers[3]

Shafiq and co workers studied two patients with the hypertrophic form of cardiomyopathy and found evidence of Type II fiber atrophy They also studied four cases of congestive cardio myopathy two of which also showed evidence of Type II fiber atrophy while a fifth case showed



Fig 4 A large collection of mitochondria with evidence of paracrystalline inclusions which have aligned in a parking lot fashion Lipid and membranous bodies are also seen × 12 000



Fig 5 Large elongated paracrystalline inclusions within the mitochondria × 12 000



Fig 6 Blurring of the Z lines and excessive folding of the plasma membrane × 22 000

what they described as a nonselective myopathy The nonselective myopathy showed evidence of internalization of capillaries in the muscle fibers and showed electromyographic myopathic activity The sixth case had evidence of a Type I hypotrophy, again with very definite myopathic involvement on electromyography

The three patients presented in this paper were referred for further study by the cardiologists because of the associated skeletal muscle abnormality It is likely that a large number of patients have skeletal muscle trouble but perhaps minimal muscular weakness is so overshadowed by their cardiologic symptoms that it goes unnoticed

In Case 1 of this paper the mitochondria are clearly abnormal The first indication that mitochondrial abnormality may account for clinical disease came with the publication of Luft and coworkers[8] in 1962, when they described a case of severe hypermetabolism of nonthyroid origin In the same year, Hoch[9] described a case of thyrotoxicosis with abnormal mitochondria In 1966 Shy, Gonatas and Perez[10] described abnormal mitochondria in the muscle of a young girl with proximal muscle weakness and referred to the

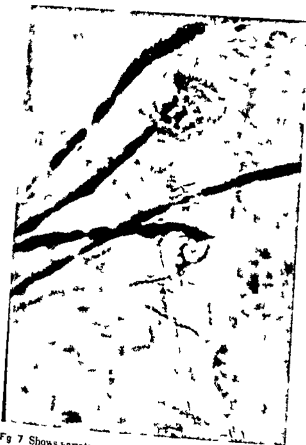


Fig 7 Shows variation in the size of the end plates together with evidence of peripheral branching of the motor nerve terminals. ×320



Fig 9 A phosphorylase preparation demonstrating marked variability in fiber size and numerous vacuoles. ×80

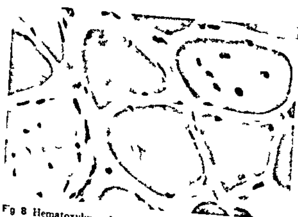


Fig 8 Hematoxylin and eosin preparation showing numerous vacuoles many of which contain nuclei ×320

condition as megaconial myopathy In the same paper these authors described a second case with abnormal mitochondria in the muscle of an 8 year old boy who suffered with slowly progressive proximal muscle wasting and weakness since birth This condition was associated with episodes



Fig 10 Marked depletion myofibrils ×10 000



Fig 11 Streaming of the Z lines and disintegration of myofibrils ×10 000

of flaccid paralysis as well as a craving for salt Electron microscopy revealed grossly abnormal mitochondria many with cristae displaying a concentric circular arrangement and the condition was named pleoconial myopathy Since this time, many cases[11] and even large families[12] have been described with myopathy associated with abnormal mitochondria [13] Price[11] produced evidence to substantiate the primary nature of mitochondrial myopathy Afifi and co workers[14] described three categories of myopathies associated with abnormal mitochondria Group 1 is characterized by hypermetabolism and myopathy, Group 2 are myopathies in which the abnormal mitochondria are the dominant feature and Group 3 includes myopathies in which the mitochondria are not the dominant pathologic feature Our Case 1 would fall into Group 2 of this classification and is the first case with this type of mitochondrial abnormality which has been linked with idiopathic cardiomyopathy It remains only an assumption that the changes seen in the skeletal muscle are also present in the cardiac muscles At this stage cardiac muscle biopsy is unjustifiable

In Case 2, the muscle weakness was considered to be due to spinal atrophy and there was good correlation between the electromyographic findings and the muscle histology, histochemistry, electron microscopy, and nerve terminal study One of the patients reported by Shafiq and co workers had evidence of neurogenic involvement of the skeletal muscle and four others showed selective Type 2 fiber atrophy Though Type 2 fiber atrophy occurs to a certain extent in cachexia and corticosteroid therapy, it is a not infrequent manifestation of neurogenic atrophy[15] and a neurogenic basis cannot be excluded in these four cases

Case 3 of this paper was found to have vacuolation of many of the muscle fibers This is a rather nonspecific abnormality and has been reported in conditions varying from acid maltase deficiency[16] to lupus erythematosus However no evidence of any specific disorder was found in this case and no clue to the etiology of the myopathy could be found on biochemical, histologic or ultramicroscopic study

From the accumulation of reported cases it is becoming obvious that striated muscle both skeletal and cardiac, may be affected in common by a host of diverse neuropathic and myopathic processes In the past such an association has been accepted for neuropathies such as Friedrich s ataxia and Refsum's disease, and one must now include spinal atrophy Myotonia dystrophica pathologically affects both nerve and muscle tissue and the heart muscle is also involved Duchenne s dystrophy though there is some evidence of a neuropathic basis is still regarded as a progressive myopathic disorder within which cardiac involvement is prominent The case of vacuolar myopathy presented in this paper is regarded as myopathy but one cannot deny that myopathic changes may be induced by some disturbance in nerve trophic activity [17] and so the primary site of pathology is debatable The myopathy with mitochondrial abnormality is regarded as a primary mitochondrial abnormality

In all these cases as stated earlier it remains an assumption that the disease process seen in skeletal muscle is similar to that giving rise to the cardiac muscle pathology It seems certain that a great deal will be learned about idiopathic cardiomyopathy when more comprehensive studies of skeletal muscle are undertaken in these cases

Summary

The skeletal muscle of three cases presenting with idiopathic congestive cardiomyopathy has been studied histologically histochemically ultramicroscopically and electromyographically In all three there is clinical evidence of skeletal muscle weakness and in all three pathologic changes were found in the muscle These changes were different in each case and varied from mitochondrial myopathy to spinal atrophy to vacuolar myopathy Other reported cases of cardiomyopathy demonstrating skeletal muscle pathology are discussed

We thank Professor J Barlow Dr Bernie Van Lingen Dr R Tucker and Dr E Gale for referring these cases

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Right bundle branch block during transvenous ventricular pacing

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Cardiac pacing through a transvenous catheter located in the right ventricle usually produces a pattern of left bundle branch block (LBBB) When right bundle branch block (RBBB) occurs during apparent right ventricular pacing a complication (perforation or malposition of the catheter) has usually occurred In the patient reported here uncomplicated right ventricular transvenous pacing produced RBBB Recognition of this uncommon event is important because it may save the patient the risk and inconvenience of repositioning a properly functioning pacing catheter

Case report

R T an 84 year old man was admitted to the hospital with a seven month history of syncope angina pectoris and congestive heart failure Physical examination showed a grade 3/6 aortic systolic ejection murmur and an absent aortic component of the second heart sound The carotid pulse upstroke was markedly delayed by palpation Roentgenograms of the chest and cardiac fluoroscopy revealed marked calcification of the aortic valve and mild enlargement of the left ventricle

The initial electrocardiogram (Fig 1) showed sinus rhythm complete atrioventricular block and an idioventricular rhythm Pacing through a transvenous bipolar electrode catheter produced RBBB An electrogram recorded from the distal electrode demonstrated a dominant S wave characteristic of recordings from the apex of the right ventricle (Fig 2) For the seven days this catheter was in place the stimulating threshold was always less than 1 0 ma No pericardial rub was heard and no complications developed

Pacing through a permanent transvenous catheter (Medtronic No 5818) again produced RBBB The stimulating threshold was 1 4 ma No complications developed in the hospital and re examination 2½ months later revealed no complications and no change in the electrocardiogram

Fig 3 shows the position of the catheters

Discussion

That these catheters were in the right ventricle is demonstrated by their position on the roentgenograms, by the appearance of the electrogram, by the constant and low stimulating threshold, by the constantly normal pacing and sensing functions, and by the absence of complications Any one of these factors alone is inadequate to insure the site of the cather tip,[1] but taken together they argue strongly for the right ventricular location of the tip

Transvenous pacing may produce RBBB if the catheter tip perforates the myocardium or ventricular septum [2-4] Stimulation from the coronary sinus often gives a RBBB configuration [1,4,5] These are probably the most common causes of RBBB during transvenous pacing

There are twelve reported cases in which RBBB occurred during uncomplicated transvenous pacing [5-8] In only seven cases was long term stable pacing maintained with this pattern, and in five of those cases, the RBBB pattern was intermittent Bauman Lamb, and Tsagaris[6] have noted two forms of RBBB in this context They described one case of classic RBBB (RV_1, S_1) and five cases of atypical and intermittent RBBB (RV_1 without S_1) Of the twelve cases of RBBB during transvenous pacing, five were of the classic type and seven were atypical

In the case reported here, pacing through the temporary catheter produced the classic RBBB pattern (Fig 2) while pacing through the permanent catheter produced the atypical RBBB configuration (not shown) This case is noteworthy because stimulation from two sites within the

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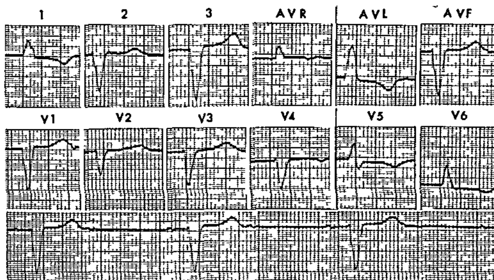


Fig 1 Electrocardiogram and rhythm strip recorded at 50 mm per second. All leads are full standard (1 mv = 10 mm.) except Leads V and V which are one half standard See Text

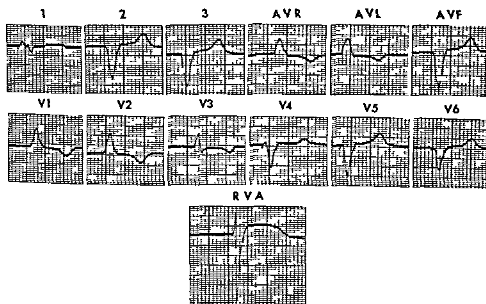


Fig 2 Electrocardiogram and electrogram recorded from the apex of the right ventricle (RVA) at 50 mm. per second All leads are one-half standard (1 mv = 5 mm) except Lead I which is full standard and Lead RVA which is one fifth standard. See text

right ventricle gave a RBBB because the RBBB was persistent and because long term stable pacing was achieved with this pattern

It is not known why right ventricular pacing sometimes leads to RBBB Preferential activation of the left bundle branch may occur through stimulation of ramifications of the left bundle branch which extend to the right side of the ventricular septum Delayed conduction in the right bundle branch may lead to RBBB during transvenous pacing [7]

When RBBB is found during transvenous ventricular pacing a complication (perforation or malposition) has probably occurred However this electrocardiographic pattern is compatible with uncomplicated pacing and repositioning the catheter may not be necessary The location of the catheter tip should be verified by viewing



Fig 3 Frontal and lateral roentgenograms of the chest showing the temporary (A) and permanent (B) pacing catheters (retouched for clarity) See text

roentgenograms, by recording an electrogram from the distal electrode, and by measuring the stimulating threshold

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Clinical pathologic conference

Massive myocardial hemosiderosis A structure-function conference at the National Heart and Lung Institute

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Arthur W Nienhuis M D
Walter L Henry M D
Victor J Ferrans M D Ph D
David R Redwood M D
William C Roberts M D
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DR. WILLIAM C ROBERTS In this conference a patient with massive myocardial iron deposition will be described and discussed Dr Arnett will present the patient s story

DR. ERNEST N ARNETT This 23 year old black man was found to have *Blackfan Diamond anemia* at 2 weeks of age and he was tranfusion dependent thereafter At *age 10 years* he received his first course of chelation therapy At *age 12* hypocalcemia was noted for the first time and a diagnosis of *hypoparathyroidism* was made At *age 15* he received chelation therapy for 8 months with removal of approximately 8 Gm of iron By age 21 he was requiring 5 units (250 ml) of packed erythrocytes every 3 weeks Splenectomy during that year reduced the transfusion requirement to 2 units every 3 weeks

At *age 22 years* he was first admitted to NIH for chelation therapy He had mild exertional dyspnea and easy fatigability when his blood hematocrit was in the low 20 per cent range He had no orthopnea nocturnal dyspnea edema or palpitations and had never received digitalis or diuretics It was estimated that he had received 500 units of packed erythrocyte transfusions equivalent to 125 Gm of iron during his lifetime The blood pressure was 90/60 mm Hg His neck was short Both eyelids drooped The cardiac apical impulse was normally located The cardiac sounds were normal and no precordial murmur was heard The liver was firm There was scant axillary and pubic hair and no subcutaneous edema The hematocrit was 22 per cent hemoglobin 7 7 Gm per 100 ml white blood cell count 10 800 per cubic millimeter with normal differential reticulocyte count 0 serum iron 188 μg per 100 ml and total iron binding capacity 200 μg per 100 ml (94 per cent saturation) The electrocardiogram (ECG) (Fig 1) showed sinus rhythm prolonged P R interval increased QRS voltage and ST T abnormalities Chest roentgenograms (Fig 2) disclosed a globular shaped heart prominent pulmonary vasculature and diffuse reticulonodular pulmonary infiltrates He remained in hospital for 5 months during which time he received many transfusions and chelation therapy Desferal (kindly supplied by Dr John Zacchio of Ciba Geigy Co) was administered as part of a metabolic balance study

Three weeks after discharge he noted mild exertional dyspnea and re examination disclosed a Grade 3/6 systolic ejection type mumur at the lower left sternal border and pedal edema An S_3 was now audible The hematocrit was 19 per cent and with three transfusions rose to 29 per cent

Following an episode of loss of consciousness at home he was readmitted to NIH a month later The hematocrit then was 17 per cent and an ECG showed multifocal premature ventricular beats prolonged P R interval and nonspecific ST T wave changes The premature beats appeared to decrease after three transfusions While sitting

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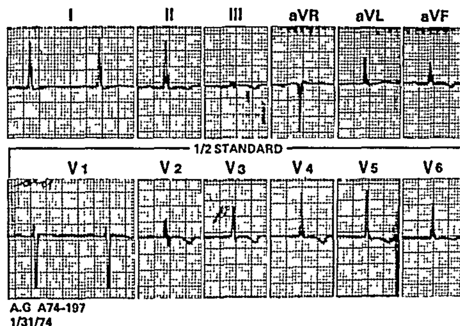


Fig 1 ECG 7 months before death and before the onset of symptoms of cardiac dysfunction It shows prolonged P R interval and diffuse ST T abnormalities



Fig 2 Posteroanterior (left) and lateral (right) chest roentgenograms 7 months before death and before the onset of symptoms of cardiac dysfunction

he had a grand mal seizure preceded by dizziness and palpitations This episode was believed to be caused by ventricular tachycardia Upon awaken ing the blood pressure was 95/60 mm Hg an S_3 was audible, and the murmur was unchanged The hematocrit was 29 per cent The ECG was unchanged He was monitored by telemetry and given quinidine gluconate Nausea and vomiting on the fourth hospital day prompted discontinua tion of quinidine Premature supraventricular beats with aberrancy, premature ventricular beats and recurrent runs of ventricular tachy cardia continued On day 7, a sustained run of ventricular tachycardia (Fig 3) led to hypoten sion and another grand mal seizure He was treated with assisted ventilation and closed chest cardiac massage and sinus rhythm returned From day 7 to day 26 he had frequent multifocal premature ventricular beats daily episodes of ventricular tachycardia, and increasing subcuta neous edema On day 26 a sustained run of ven tricular tachycardia required electroversion Chest radiograph revealed increasing congestion During the remainder of his life the arrhythmias persisted Serum potassium was frequently ele vated and on day 41 he became comatose, presumably because of severe hypoglycemia (30 mg per 100 ml) On day 47, ventricular fibrilla

Table 1 Echocardiographic observations

Time before death	*7 months*	*23 days*	*4 days*
LV transverse dimension (diastole)	50	62	63
LV transverse dimension (systole)	34	52	58
Septum	14	14	12
LV posterior wall	14	14	12
LV mass	368	516	430
Ejection fraction	69	41	22
Left atrium	31	46	41
Aortic root	23	23	22
Heart rate	74	86	88
Mitral diastolic closing rate	90	135	124
Pericardial effusion	None	None	Present

tion occurred and resuscitation was successful The hematocrit was 33 per cent He died on day 61 because of recurrence of ventricular fibrillation

DR. ROBERTS Dr Redwood could you discuss the His bundle electrogram?

DR. DAVID R REDWOOD On day 57 because of persistent runs of ectopic tachycardia which proved refractory to antiarrhythmic therapy a *His bundle electrogram* was recorded to determine the origin of the ectopic beats As can be seen in Fig 4 the normally conducted beats show prolonged (300 msec) PR interval the A H interval is markedly prolonged (210 msec) and there is also slight prolongation (70 msec) of the H V interval The latter prolongation can be attributed to procaine amide therapy During the short burst of ectopic beats no His spike preceded each ventricular complex thus confirming a ventricular origin of the arrhythmia The etiology of the first-degree A V block is uncertain but may have resulted from structural damage to the A V node by iron deposits It is unlikely that it can be attributed entirely to the pharmacologic effects of digoxin (0 125 mg daily) or of procaine amide (2 000 mg daily) The repeated runs of ventricular tachycardia are entirely consistent with myocardial damage from iron deposition

DR. ROBERTS This patient had three echocardiograms during his last 7 months of life Dr Henry could you summarize your echocardiographic observations?

DR. WALTER L HENRY The first echocardiographic study was performed 7 months before death when the patient clinically had no symptoms of cardiac dysfunction except for exertional

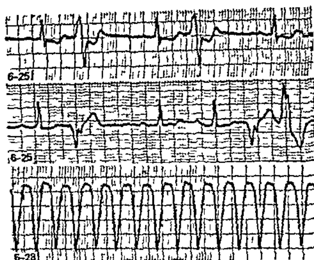


Fig 3 ECG rhythm strips" 2 months before death showing premature supraventricular beats with aberrancy multifocal premature ventricular beats and ventricular tachycardia

dyspnea and easy fatigability when his hematocrit was below 25 per cent This initial study demonstrated a nondilated concentrically thickened left ventricle (Fig 5) Systolic function appeared normal (ejection fraction = 69 per cent) but a mildly reduced rate (90 mm per second [normal = 110]) of early diastolic closure of the anterior mitral valve leaflet suggested reduced left ventricular compliance (Table 1) Left atrial aortic root and right ventricular transverse dimensions were normal There was no evidence of pericardial effusion

A second echocardiographic study was performed 6 months later (23 days *before death*) and 2 days after an episode of ventricular tachycardia hypotension and a grand mal seizure which had resulted in transient coma Compared to the initial study a marked decrease in ejection fraction (69 to 41 per cent) and increase in diastolic left ventricular transverse dimension and left atrial transverse dimension (31 to 46 mm) had occurred (Fig 5)

The final echocardiographic study was performed 4 days before death The major change from previous studies was a further reduction in ejection fraction and perhaps a decrease in septal and posterior wall thicknesses

The echocardiographic assessment of cardiac structure and function obtained in this patient are of particular interest in that they document the striking cardiac changes that may occur in some patients during the end stage of a chronic



Fig 4 Recording of His bundle bipolar electrogram (HBE) and standard ECG Lead II The normally conducted beats show prolonged AH and HV times The ectopic beats show ventricular complexes that are not preceded by His bundle spikes thus demonstrating their ventricular origin

myocardial disease In this patient, the initial echocardiographic assessment of cardiac structure revealed a nondilated concentrically thickened left ventricle Systolic function appeared to be reasonably well preserved, left ventricular compliance appeared mildly reduced At this time (i e 7 months before death), the echocardiographic measurements were similar to those obtained from patients with infiltrative cardiomyopathies due to a variety of systemic diseases

Six months later, however, a marked reduction in systolic function and marked left ventricular dilatation had occurred Whether such striking changes preceded the patient's cardiac arrhythmias and hypotension or were at least in part due to these episodes cannot be determined What is important, however, is that the final echocardiographic assessment and necropsy examination were consistent in that they both revealed a grossly dilated left ventricle whose walls were not particularly thickened Thus, if the necropsy examination and the final echocardiographic study were the only information available, one would likely conclude that iron overload due to chronic transfusion therapy primarily produced a decrease in systolic function and marked ventricular dilatation, changes similar to those seen in patients with idiopathic cardiomyopathy of the ventricular dilated type ("congestive cardiomyopathy") The echocardiographic studies from asymptomatic and minimally symptomatic patients with infiltrative cardiomyopathies as well as the initial echocardiographic study in the present patient, however, indicate that systolic dysfunction usually occurs only in the end stage of the disease process and that the initial changes that can be detected echocardiographically are a concentric increase in left ventricular mass without systolic dysfunction

DR. ROBERTS This patient was studied by Dr Nienhuis and his colleagues Dr Nienhuis could you discuss the Blackfan Diamond anemia, the possible effect on the heart of 23 years of severe anemia, and your hopes with chelation therapy as far as cardiac iron is concerned?

DR ARTHUR W NIENHUIS Blackfan Diamond syndrome, or *constitutional hypoplastic anemia*, is a congenital disorder characterized by the complete absence of red cell precursor in the bone marrow and of reticulocytes in the peripheral blood In five reported families two siblings were affected, suggesting a hereditary basis with inheritance possibly as an autosomal recessive[1] Onset may be shortly after birth, as in this patient, or may be delayed for several months Partial or complete remission has occurred in response to corticosteroid therapy, although only if treatment is instituted shortly after the onset of the disease[2,3] Androgen has been tried with little success in an attempt to stimulate the bone marrow In contrast to erythroid hypoplasia in adults there is no apparent association of Blackfan Diamond syndrome with thymoma nor have inhibitors to erythroid growth been found in the plasma Thus, constitutional hypoplastic anemia appears to be a primary disorder of erythroid tissue rendering the patient dependent on blood transfusions to sustain life

Cardiac disease in this patient reflects the combined effects of chronic anemia and progressive iron deposition in the myocardium An important pathogenic role for the iron is suggested by the fact that most patients with severe—but non-transfusion dependent—anemia do not develop symptoms of cardiac dysfunction Recently, desferrioxamine has been shown to retard hepatic iron deposition and prevent fibrosis in patients with thalassemia major indicating

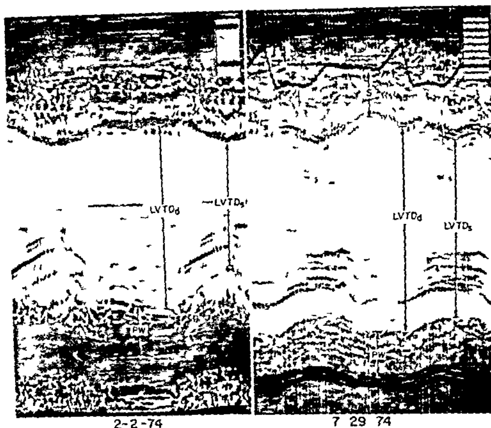


Fig 5 Echocardiographic records obtained 7 months before death (left) when the patient was asymptomatic and again 1 month before death (right) after an episode of ventricular tachycardia and hypotension The wall thicknesses that are labeled were confirmed in the damped portions of the echocardiographic tracings that are not shown in this figure. The 1 cm. calibration markers are shown in the upper right corner of each panel (Note the record in the right panel of this figure was obtained with an ultrasound instrument containing circuits especially designed to highlight the epicardial lung interface) *S* = thickness of ventricular septum *PW* = thickness of left ventricular posterior wall *LVTD* = internal dimension of left ventricular cavity at end-systole

that chelation therapy may be useful in preventing tissue damage from iron in patients requiring transfusions[4] Whether myocardial iron deposition also can be prevented remains to be determined Daily administration of Desferal to this patient resulted in excretion of 35 to 45 mg of iron per day This amounts to 1 0 to 1 3 Gm per month exceeding that given by transfusions during the period of treatment Nonetheless serious cardiac disease was not prevented indicating that irreversible myocardial iron accumulation already had occurred

DR. ROBERTS Dr Arnett could you summarize your finding at necropsy in this patient?

DR. ARNETT At necropsy serous effusions were present in the pericardial (230) pleural (right = 800 ml. left = 50 ml) and peritoneal cavities (1,200 ml) Iron deposits were present usually in huge amounts in virtually every body organ (Table II) The liver was cirrhotic portal type The thyroid gland pancreas testes and parathyroid glands were considerably scarred in addition to containing heavy iron deposits

The heart weighed 320 grams and all four chambers were dilated (Fig 6) Neither ventricular wall was thickened (right 0 4 and left 1 4 cm) The myocardium except that of the right atrium was rusty brown (Fig 6) There were no gross myocardial scars The only sites of myocardial necrosis and these were only foci of myocytolysis were the left ventricular papillary muscles (Fig 7) The four cardiac valves were normal The left ventricular endocardium was mildly thickened Except for focal iron deposits in the internal elastic membrane the extramural coronary arteries were normal

Histologic sections of ventricular and left atrial myocardium revealed heavy iron deposits in

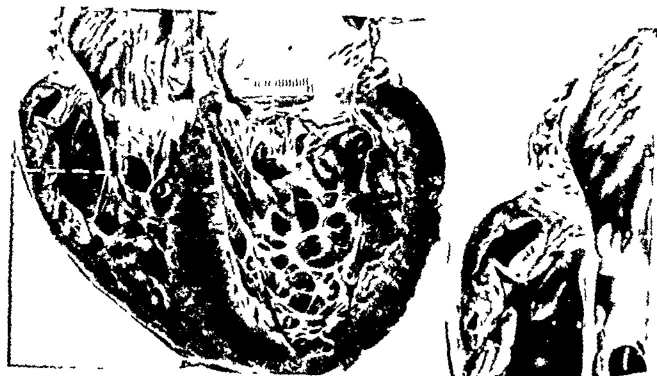


Fig 6 Interior of the heart Left Longitudinal section showing relative sizes of the chambers and their walls The myocardium of the ventricles left atrium and atrial septum is dark brown whereas that of the right atrium is much lighter indicating far fewer iron deposits Right A close up of the junction of right atrium with right ventricle to demonstrate the light color of the atrial wall in comparison to the ventricular wall

Table II Presence and amount of iron in various body organs or tissues

Organ	0 4+
Myocardium	++++
Liver (1,220 Gm)	++++
Pancreas	++++
Spleen (730 Gm)	++++
Lymph node	++++
Pituitary gland	++++
Thyroid gland (10 Gm)	++++
Parathyroid gland	++++
Adrenal gland	++++
Testis	++++
Prostate gland	++++
Stomach	++++
Kidney	++
Lung	++
Skeletal muscle	+
E ophagus	0
Small intestine	0
Large intestine	0
Central nervous system	0

virtually every working myocardial cell (Fig 8) *Iron deposits were greatest in the epicardial third* and papillary muscles, intermediate in the endo cardial third and least *in the middle third of the* left ventricular wall *Focal myocytolysis* was extensive in *the papillary muscles, these* collec tions of myocardial cells consisted only of nuclei

Table III Myocardial iron content

	µg/Gm
Right atrium	119
Right ventricle	1,891
Left atrium	254
Left ventricle (LV)	2,362
Endocardial ⅓ of LV	1 409
Epicardial ⅓ of LV	3 498
Ventricular septum	2 192

sarcolemmal sheaths and intracellular iron, the myofibrils and other organelles had vanished (Figs 9 and 10) In preserved myocardial cells iron deposits were heaviest around the nucleus, but filled a large part of many cells (Fig 10) Sections of right atrial myocardium revealed only scattered, small, iron deposits (Fig 11) Serial sections of A V node, A V bundle, and the prox imal right and left bundle branches revealed only small focal iron deposits in the conducting cells *(Fig 12) as contrasted to the heavy deposits in the* contracting myocardial cells Iron primarily in *alveolar spaces accounted for the* reticulonodular pattern of the lung by chest roentgenogram (Fig 13)

Iron content of myocardium from the walls of all four chambers was determined by atomic absorption spectrophotometry This analysis



Fig 7 Histologic sections of left ventricular wall and papillary muscle Left Hematoxylin and eosin stain showing extensive areas (pale) of myocytolysis in papillary muscle Right Iron stain showing the heavy deposition of iron in the papillary muscle and the epicardial third of free wall

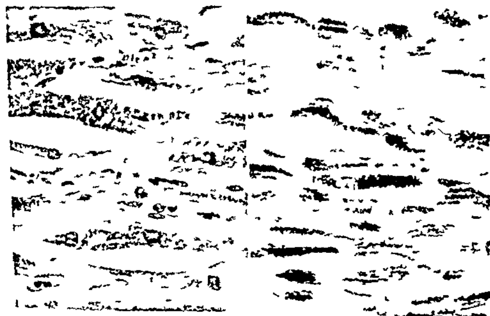


Fig 8 Histologic sections of left ventricular myocardium showing extensive iron depositions Left Hematoxylin and eosin stains, Right Iron stain (Each ×560)

again disclosed that the deposition of iron was least in the right atrial myocardium and that within the left ventricular wall iron was more heavily deposited in the epicardial half than in the endocardial half (Table III)

DR. ROBERTS Electron microscopic examination of myocardial cells was performed by Dr Ferrans who will summarize his observations

DR. VICTOR J FERRANS The left ventricular myocardial cells examined ultrastructurally con



Fig 9 Histologic section of left ventricular papillary muscle showing degenerated myocardial cells consisting only of sarcolemmal sheaths nuclei, and heavy iron deposits (Hematoxylin and eosin stain ×880)

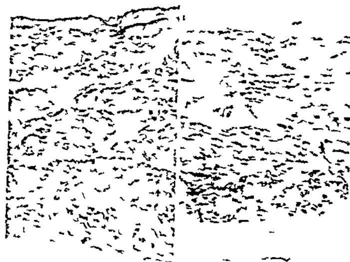


Fig 11 Histologic sections of atrial walls Left Right atrium containing few iron deposits Right Left atrium containing heavy iron deposits (Each ×54)

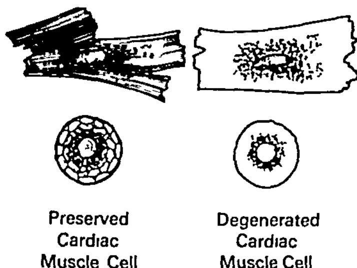


Fig 10 Diagram showing both preserved and degenerated cardiac muscle cell containing iron deposits Relatively few severely degenerated muscle cells were observed in comparison to the preserved cells The amount of iron deposition in each appeared to be similar suggesting that another factor possibly anemia was responsible for the disappearance of the myocardial fibers and filaments in the degenerated cell rather than the iron deposition

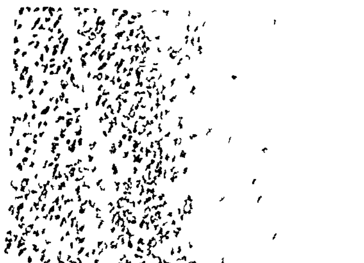


Fig 12 The conducting tissue (as shown on right) contained much less iron than the working myocardium (as shown on the left) The conducting tissue shown here is a portion of the His bundle (Hematoxylin and eosin stain ×140)

tained large numbers of aggregates of iron particles, decreased numbers of mitochondria and myofibrils and scattered concentric lamellae presumed to be derived from products of mitochondrial breakdown (Fig 14)

Dr Roberts Until recent years there was considerable debate whether or not infiltration of iron into myocardial cells could cause them to function abnormally It is now clear beyond any reasonable doubt that myocardial hemosiderosis can cause myocardial dysfunction [5] Whether or not dysfunction results is dependent on the amount of iron entering the myocardial cells huge amounts as occurred in the patient described herein may produce congestive cardiac failure and arrythmias small amounts of myocardial iron cause no evidence of myocardial dysfunction [5]

In patients with cardiac hemosiderosis certain areas of the heart contain heavier deposits than do other areas The ventricular free walls and ventricular septa contain heavier deposits of iron than do the atrial walls Of the various myocardial walls infiltrated by iron, the right atrial one—as so clearly demonstrated in the present patient—contains the least The amount of iron in the various layers of ventricular myocardium also

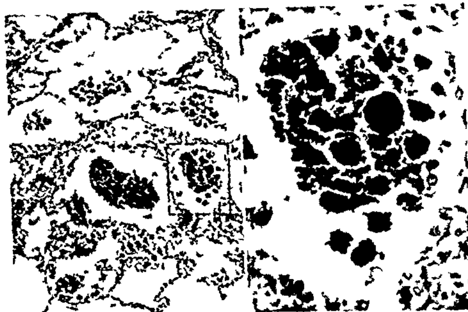


Fig 13 Sections of lung disclosing heavy deposits of hemosiderin laden macrophages in many alveoli. The right photomicrograph shows a single alveolus containing many iron filled macrophages (Hematoxylin and eosin stains ×140 [left] ×560 [right])

is variable the epicardial third and the papillary muscles contain the most the middle third the least and the subendocardial third intermediate between the two The conduction tissue is relatively spared by iron deposits as compared to the contracting myocardial cells.[5] Serial sections of sinus node A V node and bundle and proximal right and left bundle branches in the present patient and in those described previously from this laboratory[5] disclosed only small deposits of iron in the conducting tissues compared to heavy deposits in the contracting myocardial cells

It would be difficult in the present patient with cardiac hemosiderosis to attribute the various atrial and ventricular arrhythmias to the presence of the few deposits of iron in the conducting tissues The altered myocardial contracting cells more likely are the source of the arrhythmias Support for this view also is provided by the His bundle electrogram which showed complete lack of impulse transmission through the His bundle prior to occurrence of ventricular ectopic beats

The reason for the differences in the amounts of iron deposited in the various portions of heart is uncertain Clearly there is something different about the myocardial cells in the right atrium compared to those in the left atrium or in either ventricle

The mechanism by which iron enters myocardial cells also is unknown The deposits are most extensive in the perinuclear areas Usually the myocardial contractile elements were fairly well preserved

The occurrence of extensive foci of myocytolysis in the left ventricle of the present patient is probably more related to the occurrence of prolonged severe anemia than to the presence of iron deposits in the myocardial cells

Dr Nienhuis raised the issue as to how much of the myocardial dysfunction in the present patient resulted from the associated severe anemia and how much from the presence of myocardial hemosiderosis The answer in the present patient is uncertain but other patients with similarly severe degrees of cardiac hemosiderosis and myocardial dysfunction have been observed in the absence of anemia[5] The present patient was anemic his entire life and evidence of cardiac dysfunction did not appear until about 6 months before death Possibly chelation therapy during his last 6 months also had a deleterious effect on myocardial function

The echocardiographic studies by Dr Henry clearly show that dilatation of the cardiac ventricles is a late manifestation of cardiac hemosiderosis and that the ventricular cavities are of normal size before evidence of myocardial dysfunction appears



Fig 14 Electron micrograph of part of left ventricular muscle cell (upper) shows large numbers of aggregates of iron particles (*IP*) decreased numbers of mitochondria (*M*) and myofibrils (*MF*) and scattered concentric lamellae (*CL*) presumed to be derived from products of mitochondrial breakdown Area within rectangle is shown at higher magnification below The iron deposits in myocardium are composed of aggregates of electron dense particles which measure from 90 to 100 A in diameter (×11 750 upper ×46 000 lower)

Cardiac hemosiderosis is never an isolated occurrence Iron deposits also are always present in most of the other body organs In the present patient and in several others reported[5] the amount of iron in the heart is roughly proportional to that in the other body organs Surprisingly in contrast to its effect on the liver, for example cardiac iron deposition does not produce a fibrous tissue reaction Possibly the reason is due to its deposition nearly entirely *within* the myocardial cells and not within the interstitium as may occur in the liver

In summary, extensive deposits of iron in the heart from whatever source—either endogenous or exogenous (as in the present patient > 500 blood transfusions)—may result in severe myocardial dysfunction Thus *the iron heart is not a strong heart but a weak one*

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Pericarditis of myocardial infarction Review of the literature with case presentation

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Pericarditis may complicate acute myocardial infarction in two forms—a more common early form occurring within 24 to 72 hours of acute myocardial infarction[1, 2] and a late form occurring usually after a week to as late as 2 years after myocardial infarction[3] The late form is known either as postmyocardial infarction syndrome or as Dressler s syndrome after Dressler who described it first The early form usually is a transient and benign condition The postmyocardial infarction syndrome (PMIS) often requires treatment for intractable chest pain, pericardial and pleural effusion etc Three cases of PMIS with different modes of presentation are described, and the syndrome is reviewed in light of recent literature

Early pericarditis in acute myocardial infarction

The incidence of early pericarditis after acute myocardial infarction as determined clinically by the presence of an audible friction rub varies from 7 to 16 per cent[5, 10] Autopsy incidence varies from 13[11] to 45 per cent[1]

Many patients with the early form of pericarditis have no chest pain or may experience dull ache which they may attribute to their myocardial infarction Therefore a proper history with regard to the presence of type of chest pain and frequent auscultation may yield a higher incidence of early pericarditis in acute myocardial infarction Frequent auscultation is necessary because the rub is usually fluctuating in character Clinical studies reveal that in 92 per cent of patients the rub appears within 4 days of acute myocardial infarction (usually on the second or third day)[4] Persistence of a rub beyond 3 days is said to carry a poor prognosis[9] The presence of a rub in early pericarditis signifies that the myocardial infarction is transmural and has involved the epicardial surface which is responsible for the appearance of the friction rub, therefore no rub is heard in patients with acute subendocardial infarction[12] The incidence of complications such as arrhythmias, congestive heart failure and shock is higher in the pericarditis group as compared to patients with acute myocardial infarction without pericarditis[8, 9] This is attributed, not to the presence of pericarditis per se but to the greater extent of myocardial damage that is seen in this group of patients as compared to those patients with acute myocardial infarction but without pericarditis Despite a high incidence of these complications the mortality rate is not significantly increased in the pericarditis group as compared to the group without pericarditis provided that they are treated under the appropriate hospital setting[8, 9]

ECG changes Apart from the arrhythmias and heart block the electrocardiogram (ECG) may be helpful in predicting the development of subsequent pericarditis in acute myocardial infarction Recently it has been shown that the degree of ST segment elevation in acute myocardial infarction bears a close correlation to the extent of myocardial damage and that pericarditis is more common in those patients who had shown initial higher ST segment elevation due to infarction[10] This finding is in conformity with the animal experimental studies of Wégria and co workers[14] These workers showed that the degree of occlusion of a coronary artery produced experimentally was closely correlated to the degree of ST segment elevation Later Maroko and associates[15] again using animal experimental models, showed a good correlation between the degree of

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coronary occlusion ST segment elevation and myocardial damage as determined by the elevation of serum enzymes of myocardial origin Higher enzyme elevations have also been noted in patients with acute myocardial infarction and pericarditis compared to those without pericarditis[8 1] Thus clinical and experimental studies would favor the conclusion that pericarditis in acute myocardial infarction signifies a greater extent of myocardial damage and the latter would account for the higher incidence of complications seen in this group of patients

Pericardial effusion in early pericarditis *Detectable effusion is rare in early pericarditis due to acute myocardial infarction* [1 18] Hemopericardium may develop as a complication of anticoagulant therapy[19 1] In one series of patients with acute myocardial infarction[9] 13 patients with pericarditis and 35 patients without pericarditis were given anticoagulants Two cases *of fatal hemopericardium developed in the anti*coagulated group compared to none in the group not receiving anticoagulants In another similar study comprising 52 patients with pericarditis and 100 patients without pericarditis no complication of effusion was noted. The authors of the latter study concluded that the presence of early pericarditis in acute myocardial infarction is not a contraindication to anticoagulant therapy However in view of some reports of hemopericardium associated with the use of anticoagulants in patients with acute myocardial infarction [9 20] it would seem wise to withhold anticoagulants when pericarditis develops in these patients Also since the role of anticoagulants in the early phase of acute myocardial infarction is confined to the prevention of thromboembolic complications the risk of prophylactic anticoagulation may outweigh benefits in patients with acute myocardial infarction and early pericarditis One may probably use anticoagulants in this setting for those at high risk of developing thromboembolic complications provided one is aware and is prepared to deal with the rare complication of tamponade should this occur Distention of neck vein Kussmaul sign pulsus paradoxus of more than 10 mm Hg rising central venous pressure a falling systolic blood pressure narrowing pulse pressures an enlarging cardiac silhouette on chest x ray and total electrical alternans in the ECG all indicate the presence of significant compressing effusion [1] The use of echocardiography for detection of pericardial effusion is not only reliable but also atraumatic[25] Other available methods for detection of pericardial effusion include CO and dye angiographic studies[1 26] Pericardiocentesis should be reserved for rare cases for diagnostic as well as therapeutic purposes

Treatment The treatment of early pericarditis is symptomatic Analgesics (aspirin acetaminophen) for chest pain may suffice and only occasionally will there be a need for more potent anti inflammatory agents (indomethacin steroids) or narcotic agents (codeine morphine or meperidine) When pain is refractory to these agents stellate ganglion blockade has been used[27] In order to avoid error in therapy one has to be careful to differentiate between myocardial dilatation and pericardial effusion[28] For the rare case of tamponade pericardiocentesis may be a life saving procedure Details of this procedure have been previously described[24 28]

Postmyocardial infarction syndrome (PMIS)

In 1955 Dressler[3] described a syndrome of pericarditis which occurred from 10 days to as late as 2 years after acute myocardial infarction Classically several weeks after acute myocardial infarction a patient presents again with the complaints of fever and chest pain and is often mistaken for having developed a new myocardial infarction The postmyocardial infarction syndrome (PMIS) *as described by Dressler[3] occurs* with an incidence of 1[9 29 3] to 4 per cent and has the following features (1) fever (2) chest pain, (3) evidence of pericarditis, (4) pulmonary involvement–pleuritis pneumonitis and (5) tendency to recurrence Three case reports of PMIS with different modes of presentation are reported here and the syndrome is reviewed in light of recent literature

Case reports

Case 1 A 58-year-old man was admitted to The Memorial Hospital with a history of severe substernal chest pain of sudden onset He had no previous history of heart disease On admission he was noted to be diaphoretic and in moderate distress. There was no jugular venous distention, the lungs were clear and the heart revealed a regular rhythm at a rate of 85 beats per minute The heart sounds were normal and there was no gallop murmur or rub The ECG was consistent with acute anterior myocardial infarction This was documented by subsequent enzyme studies (SGO LDH HBD CPK) The chest x ray revealed a normal heart size and clear lung fields.

Hospital course The course was uncomplicated and he

remained free of symptoms of chest pain or dyspnea On the twentieth day after his infarction the patient experienced severe chest pain with profuse diaphoresis The blood pressure was 110/70 mm Hg the pulse *was 110 b p m and regular and* he was afebrile He was thought to have suffered another myocardial infarction and was transferred to the coronary care unit A loud triphasic friction rub was heard diffusely over the precordium by at least two physicians and some medical students The FCG revealed diffuse ST segment elevations consistent with pericarditis The chest x ray revealed an enlarged cardiac silhouette with evidence of left pleural effusion A CO atriogram was performed and was *reported to be* consistent with pericardial effusion The diagnosis of PMIS was made and the patient was started on prednisone 40 mg per day orally Over a period of approximately 7 days the chest pain disappeared the friction rub became inaudible and the chest x ray *revealed a decrease in* the heart size and clearing of left pleural effusion The patient was transferred out of the coronary care unit and to the regular floor for further convalescence

Comments This case represents a classical picture of post myocardial infarction syndrome as described by Dressler The response to steroids was excellent as noted by Dressler and other *workers*

Case 2 A 62 year old man was admitted to The Memorial *Hospital on Jan 25 1974 with chief complaints of severe* substernal chest pain accompanied by shortness of breath and diaphoresis The pain radiated to both sides of the shoulder the neck and the left arm He was known to be hypertensive and was taking antihypertensive medication

Physical examination revealed that the patient was in moderate distress The blood pressure was 140/70 mm Hg the pulse was 82 b p m and regular the respiration was 20 per minute and he was afebrile There was no jugular venous distention Minimal fine rales were *heard bilaterally* The heart showed a regular rhythm with normal heart sounds There was no gallop murmur or rub The rest of the physical examination was essentially unremarkable

The ECG on admission was consistent with acute infero lateral myocardial infarction This was further documented by significant elevations of enzymes (SGO LDH HBD CPK) The initial sedimentation rate (ESR) was 12 mm per hour The white cell count was 11 900 with a slight shift to the *left*

The chest x ray revealed mild congestive changes without evidence of effusion There was left ventricular preponderance

Hospital course On Jan 27 the patient complained of continuous chest pain which was different in character from the one he had described on admission This pain was sharp and was aggravated by deep breathing and coughing It was partially relieved by leaning forward The patient required repeated medication for pain (morphine) The blood pressure was 130/"0 mm Hg with a pulsus paradoxus of 10 mm Hg The temperature at this time was 100 8 F Auscultation revealed a classical triphasic friction rub The ESR was 115 mm per hour The ECG revealed diffuse ST segment elevations consistent with pericarditis The chest x ray showed generalized cardiomegaly infiltrate at the left base and left pleural effusion Cultures of the sputum and blood were taken and the patient was started on antibiotic cephalothin (Keflin) Also heparin prophylaxis *on which* the patient had been started since admission was stopped It should be noted however that neither his clotting time nor the partial thromboplastin time was in the therapeutic range A CO atriogram *was performed which was consistent with significant* pericardial effusion Up until this time the patient had been receiving treatment for heart failure with digoxin and diuretic furosemide (Lasix) without having shown any significant improvement in his condition He was started on steroids i e prednisone 40 mg per day orally Within a week he was afebrile the chest pain had disappeared the rub was heard only intermittently and the ESR had come down to 48 mm per hour The ECG revealed evolutionary changes of inferolateral myocardial infarction and the ST changes of diffuse pericarditis had almost disappeared The chest x ray revealed a decrease in the heart size and disappearance of effusion A repeat CO study was consistent with decrease in pericardial effusion Despite *his improvement the patient continued to show manifesta*tions of heart failure with occasional episodes of typical angina relieved by sublingual nitroglycerin He was discharged on March 8 on digitalis diuretics and prednisone 5 mg three times a day

Comments This patient developed a classical picture of PMIS within a week of the diagnosis of acute myocardial *infarction Although heparin might be incriminated as an* etiologic factor in the precipitation or aggravation of pericar*dial effusion this seems unlikely in view of normal clotting* time and partial thromboplastin time His response to steroids was remarkable However the patient continued to show manifestations of heart failure and angina due to coronary artery disease

Case 3 A 52 year old man was brought to the hospital in a comatose state by the rescue squad The wife stated that he had complained of substernal pressure like sensation while they were out driving Suddenly the patient was noted to have slumped on the steering wheel and they were *involved in a* minor accident with another car No one was seriously injured in the accident but the patient was noted to have regained consciousness and had continued to complain of substernal pressure like pain At this time he was noted to be diaphoretic The rescue squad was summoned and when the patient reached the emergency room he was again noted to have lost consciousness He was found to be in cardiac arrest (ventricular fibrillation) from which he was successfully resuscitated by DC shock *The ECG revealed extensive acute anterior* myocardial infarction Subsequent enzyme studies revealed marked elevations of SGO LDH CPK and HBD The ESR was noted to be 100 mm per hour The WBC was 16 000 with a slight shift to the left Serum potassium was 3 2 mg per liter The chest x ray was reported to be within normal limits The patient was treated with lidocaine and potassium supplementation for recurrent ventricular premature beats He remained free of chest pain and dyspnea but on the third day he experienced *severe substernal chest pain* which was aggravated by deep breathing and coughing and was partially relieved by leaning forward The blood pressure was 110/65 mm Hg with a pulsus paradoxus of 5 mm Hg The temperature was 100 F the pulse was 115 b p m and regular A loud triphasic friction rub was heard *by several observers There* was no evidence of congestive heart failure but an S gallop was heard intermittently A low grade fever continued The ECG showed no changes from the initial one The chest x ray at this time revealed the presence of an infiltrate in the right

lung field The ESR was 46 mm per hour The WBC was 21 000 with a marked shift to the left The patient received morphine for chest pain Cultures of sputum blood and urine were taken and he was started on antibiotic (cephalosporine) Two days later the patient s chest x ray was reported to show another infiltrate in the left lower lobe and a left pleural effusion The heart size had not changed and there was no evidence of congestive heart failure The ECG was unchanged On the third day after the appearance of rub the patient complained of unbearable chest pain which was aggravated by minimal activity in bed Close questioning and examination revealed that he had besides the pericarditis pain left shoulder pain and tenderness This was attributed to either musculoskeletal sprain or probably atypical gouty arthritis (uric acid 8 6 mg /dl) X ray of the shoulder was reported to be normal Because of the shoulder pain and because of persistent chest pain friction rub and repeated requirements of morphine he was started on indomethacin (Indocin) 25 mg by mouth, three times a day There was a dramatic response to this medication in that the chest pain and the shoulder pain disappeared within 2 days The friction rub was audible intermittently and faintly for the next 5 days After 5 days of treatment with indomethacin the chest x ray revealed clearance of the pulmonary infiltrates and the pleural effusion Besides indomethacin the patient was receiving propranolol (Inderal) and digoxin for control of persistent sinus tachycardia with intermittent S gallop The remainder of this hospital stay was uneventful and he was discharged to his home on maintainance digoxin

Comments Two days after cardiac arrest due to acute myocardial infarction the patient developed chest pain and a loud pericardial friction rub He also developed pain and tenderness of the left shoulder which was probably musculo skeletal in origin or perhaps due to atypical gouty arthritis The pericarditis pain shoulder pain and tenderness and pul monary infiltrates responded dramatically to indomethacin

Discussion

Three cases of PMIS are described each with a different mode of presentation Case 1 belonged to the classical syndrome of PMIS as described by Dressler Case 2 is unique in that the patient presented with all the features of PMIS on the third day of acute myocardial infarction The patient in Case 3 also presented with features of PMIS within a week of infarction including pulmonary infiltrates and pleural effusion but without evidence of detectable pericardial effu sion The following discussion will focus on the main features of PMIS and a review of recent literature pertaining to the syndrome

Time of onset Although Dressler noted that the syndrome occurred from 10 days to 2 years after acute myocardial infarction recent reports as well as Cases 2 and 3 reported here indicate that the syndrome may appear within a week of myocardial infarction Also careful review of Dressler s series reveals that one of his patients (Case 2) may have developed the syndrome much earlier since he was noted to have a pericardial friction rub on the second day of acute myocar dial infarction The rub persisted beyond 2 weeks at which time pericardial effusion was noted Since effusion is considered to be one of the main features of PMIS and since the chest x ray is not reliable in detecting minimal pericardial effusion it is possible that at least a few cases of PMIS are not diagnosed earlier It is also possible that a few patients who show persistence of chest pain and rub are treated with anti flammatory agents thus aborting the full blown picture of PMIS This may have been the case in the patient (Case 3) reported here in whom there was no evidence clinically or by chest x ray of detectable pericar dial effusion It is possible that with more sensi tive and noninvasive methods available today especially in the form of echocardiography, minimal pericardial effusion may be detected and may aid in the diagnosis of PMIS in the appro priate setting

Proper history for the type of chest pain (see below) and frequent auscultation for the detec tion of friction rub may aid one to make the correct diagnosis Otherwise one is more liable to diagnose new infarction or reinfarction in this group of patients because of similarity of clinical presentation i e chest pain diaphoresis etc as was noted in here in Case 1

Chest pain The nature of chest pain is the same as that described for early pericarditis of acute myocardial infarction and other forms of acute pericarditis Chest pain due to pericarditis is aggravated (or occasionally brought on) by deep breathing coughing sneezing swallowing or yawning [2, 26] The patient may lean forward seeking relief from pain perhaps because of the splinting action afforded by this position A patient who is having pain due to acute myocar dial infarction more commonly prefers to lie backward or even flat in bed (unless he has dyspnea due to left ventricular failure) Although coronary pain may radiate to the cervical area pain due to pericarditis typically radiates to the trapezius ridge which is supplied by the phrenic nerve which also innervates the pericardium [2] In addition to the phrenic nerve (C3 4 5) the pericardium has additional pain pathways (C7 T1) This is suggested by the finding that stellate ganglion blockade (C7 T1) has been shown to relieve pain due to pericarditis [2]

Pain due to pericarditis in PMIS may respond to simple measures as noted in the early form of pericarditis If effusion complicates the picture or if the pain is refractory to simple analgesics a short course of steroids is favored by many workers because of the dramatic and almost predictable results[33, 34] Other agents which are beneficial in this condition include indomethacin,[32] butazolidine,[24] or, rarely, an antimetabolic agent (6 MP)[4] In the cases described here steroids were used in Cases 1 and 2 and indomethacin in Case 3 all with good results

Pericardial effusion The nature of pericardial effusion has been described to be serous, serosanguineous or hemorrhagic[3] It has been suggested that the typical effusion of PMIS is serous and that the effusion in the earlier phase of myocardial infarction may be hemorrhagic due to the complication of the transmural infarction itself, which may cause some bleeding over the surface to render the effusion bloody[31] Cytologic studies of the effusion in one case report indicates that it may be inflammatory in nature because of a neutrophilic preponderance[31] Hemorrhagic pericardial effusion is noted by some to reflect a complication of anticoagulant therapy[8, 19, 23] Cultures of the effusion for bacteria, including acid fast bacilli and viral studies have been negative L E cells, cold agglutinins heterophile antibodies ANA, and latex RA have also been reported negative[3, 31] Recent immunologic studies of the effusion are described later in the discussion

Pleuritis and pleural effusion Among the 35 patients reported by Dressler an incidence of 68 per cent of pleural involvement with effusion was noted The nature of the effusion was the same as described for pericardial effusion with the latter being more predominant Dressler found no evidence of pulmonary infarction in his group thus ruling out the possibility of pulmonary thromboembolism with infarction as the cause of effusion An immunologic etiology has been attributed to account for pleural effusion (see below) As in pericardial effusion, therapy with steroids brings dramatic improvement This was noted by Dressler and was also noted in Cases 1 and 2 as described here As noted earlier, indomethacin was effective in Case 3

Pneumonitis In his series of 35 patients Dressler described an incidence of 28 per cent for pneumonitis According to Dressler the lung pathology is noted on the chest x ray as pulmonary infiltration, either linear or in patches, mostly located in the bases In his series, although a few patients presented with hemoptysis, no evidence of pulmonary infarction was noted Response to antibiotics was poor and that to steroids was dramatic Recently, in a case report of five patients with PMIS with pneumonitis, Weiser and co workers[35] concluded that pneumonitis of PMIS is attributed to an unusual manifestation of severe left ventricular failure and denotes a poor prognosis For therapy, they recommended aggressive measures to combat left ventricular failure rather than steroid therapy, which was tried without success in one of their cases Earlier Geever and associates[16] had described 'atypical pulmonary inflammatory reactions in patients dying of cardiac disease due to different etiologies Dressler commented on three of Geever's cases of pneumonitis following myocardial infarction All had evidence of pericarditis and therefore fit the diagnosis of PMIS (with pneumonitis) as described by Dressler Weiser and co workers however, commenting on the same series of Geever and drawing on their own postmortem studies of patients with PMIS and patients dying of heart failure due to various cardiac causes attributed the typical histologic findings to an unusual form of heart failure rather than to an immunologic phenomenon In addition they stated that the improvement in the lung lesions as noted by Dressler was due to the concomitant therapy for heart failure rather than to steroids In Case 3 described here the x ray revealed pulmonary infiltrates and pleural effusion Although pulmonary infiltrates could have signified the presence of pneumonia there was no response to antibiotic therapy and the cultures taken prior to commencement of antibiotic therapy showed normal flora Also there was no response to digitalis and diuretic therapy These infiltrates cleared dramatically after commencement of therapy with indomethacin an anti inflammatory agent As already noted similar striking responses have been observed after therapy with steroids It would therefore appear that further studies are needed to determine the exact etiology of the pulmonary infiltrates in patients with PMIS

Etiology of PMIS Dressler[3] thought that the syndrome was a result of an immune disorder secondary to injury of cardiac tissue Viral etiology has also been suggested[31] Recent immuno

logic studies would seem to indicate an immuno logic cause for PMIS Heart specific antibodies have been detected in patients with the related condition of postpericardiotomy syndrome[39,40] and in patients with PMIS[4] It has been further shown that although these antibodies are also seen in other cardiac disorders[41,42] their titer was less than 2+ [2] and that a titer of 2+ fluorescent positivity or greater was found exclusively in patients with PMIS and postpericardiotomy syndrome [1] It has been suggested that the site of immunologic reaction lies in the pericardial space [1] Inflammation or blood in the pericardial space causes the epicardium to show an immuno logic response whereby pericardial effusion occurs It has been further suggested that the pleural effusion occurs as an adjacent or neigh borhood" response of the pleura since there is no involvement of distant serous membranes[4] Thus it would appear that immunologic studies i e detection of heart specific antibodies in higher titers may aid the diagnosis of PMIS

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Electrophysiology and pharmacology of cardiac arrhythmias IX Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade Part C

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Cellular electrophysiological effects of beta receptor blocking drugs and possible mechanisms of antiarrhythmic action

Ascribing mechanisms of antiarrhythmic action to effects of beta receptor blocking drugs on cellular electrophysiology is more complex than for the other antiarrhythmic agents which we have discussed All beta receptor blocking drugs prevent catecholamine induced alterations of the transmembrane action potential and this undoubtedly can exert an important antiarrhythmic effect In addition certain of these drugs (propranolol alprenolol) exert direct membrane effects on cardiac fibers independently of beta receptor blocking action and the extent to which these direct effects contribute to *clinical* antiarrhythmic activity is uncertain

Many studies have described the antiarrhythmic effects of a wide variety of beta blocking drugs on experimental cardiac arrhythmias in laboratory animals All beta receptor blocking drugs whether or not they possess direct membrane actions are effective in preventing arrhythmias provoked by catecholamine administration The d isomers of beta blocking drugs with direct membrane actions (d isomers retain the direct membrane effect but are devoid of beta receptor blocking properties) are ineffective against these arrhythmias Therefore in this case the antiarrhythmic effect is due to the beta receptor blockade Beta receptor blocking drugs without direct membrane actions prevent many of the arrhythmias which result from activation of the autonomic nervous system and this antiarrhythmic effect is also due to beta receptor blockade[2,3] However certain of these arrhythmias are not prevented by beta blockade[4,6] and Gillis has postulated that a noncatecholamine substance may be released from sympathetic nerves and may also be arrhythmogenic[5] Beta receptor blocking drugs devoid of a direct membrane effect may also prevent the ventricular arrhythmias which occur within minutes after coronary artery ligation[3] Only beta receptor blocking drugs with direct membrane effects abolish the ventricular arrhythmias which occur in the dog 24 to 48 hours after coronary ligation[7] and only beta receptor blocking drugs with direct membrane actions can abolish arrhythmias due to digitalis toxicity in experimental animals In many studies the d isomers have been as effective as the racemic mixture against both types of arrhythmias[1,8,9] From these experimental observations it has been concluded that the antiarrhythmic efficacy of beta receptor blocking drugs against arrhythmias induced by digitalis and myocardial infarction is due to the direct membrane effects

That direct membrane effects of certain beta receptor blocking drugs undoubtedly are responsible for the antiarrhythmic actions against certain experimental arrhythmias does not neces

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sarily mean that a direct effect is necessary for clinical antiarrhythmic actions If a direct membrane action were necessary, clinical effectiveness of beta blocking drugs lacking a direct membrane action should be limited to arrhythmias caused by effects of the sympathetic nerves on the heart and clinical effectiveness should differ from that of drugs which have direct membrane effects However the spectrum of clinical effectiveness of drugs without direct membrane effects seems to be the same as that of drugs with membrane effects Drugs without direct membrane effects such as practolol have been successfully used in humans to treat digitalis induced and myocardial infarction arrhythmias[10] even though experimental studies indicate that only drugs with direct membrane actions should be effective In humans beta receptor blockade alone could account for clinical effectiveness of beta blocking drugs against responsive arrhythmias including those resulting from digitalis intoxication and myocardial infarction since both these latter arrhythmias have a sympathetic component In the experimental animal which often is anesthetized during drug trials,[9] the sympathetic nervous system may not be important in the genesis of these arrhythmias

In humans the antiarrhythmic plasma levels of beta blocking drugs with direct membrane actions such as propranolol, are much lower than the drug concentrations needed in vitro to produce direct effects on the transmembrane potentials of normal cardiac cells [10] This observation also seems to favor, but is not definitive proof of a beta receptor blocking mechanism for antiarrhythmic action The possible contributions of membrane effects of metabolites of propranolol to its antiarrhythmic actions is not yet known Beta receptor blocking drugs with direct membrane actions may also affect the transmembrane potentials of diseased cardiac fibers at much lower concentrations than are needed to directly affect normal fibers Therefore even though the antiarrhythmic effects of the beta receptor blocking drugs could be explained entirely by beta receptor blockade, the importance of the direct membrane effect of some of these drugs cannot be discounted We will therefore describe the electrophysiologic effects of beta receptor blocking drugs which are due both to beta receptor blockade and to direct effects and indicate how either can be antiarrhythmic

Effects on conduction of the cardiac impulse effects on resting membrane potential, action potential amplitude and rate of depolarization during phase 0 (V_{max}) The effects of beta receptor blockers on conduction depend on several factors including (1) whether catecholamines are present and if so, the effects the catecholamines are exerting on the action potential (2) the type of tissue and its condition i e, are action potentials normal or are they depressed and (3) the presence or absence of direct effects of the drug

In concentrations low enough to cause beta receptor blockade but no direct membrane effects beta receptor blocking drugs do not alter the normal resting membrane potential action potential amplitude, or V_{max} of atrial, Purkinje or ventricular muscle fibers [11 14] When, in such fibers values for these parameters are abnormally low, catecholamines may increase them In this case beta receptor blockade might depress conduction by removing the catecholamine effect In the presence of high [K] catecholamines induce slow response action potentials The upstroke of these slow responses can be markedly depressed by beta receptor blockade and conduction blocked This effect might be one mechanism by which beta receptor blockade could abolish reentry resulting from slow responses and may be particularly important in arrhythmias during the early stage of myocardial infarction

Propranolol and alprenolol also have direct membrane effects which are exerted at concentrations 10 to 100 fold higher than are necessary for the beta blocking action At concentrations of 3 μg/ml and greater these drugs depress V_{max} action potential amplitude, the membrane responsiveness curve and conduction in normal atrial ventricular, and Purkinje fibers [11 15 17] Resting membrane potential is not altered (Fig 1) These effects probably result from actions of these drugs to decrease Na conductance [18 19] The concentrations in perfusates which depress the normal action potential are far higher than the antiarrhythmic blood levels in humans However it is possible that much lower concentrations would exert a direct effect on diseased fibers Also we do not know if these drugs exert a direct effect on V_{max} of phase 0 and conduction of slow response action potentials which are not dependent on catecholamines To the extent that a direct depressant effect on conduction is responsible for antiarrhythmic activity these drugs may

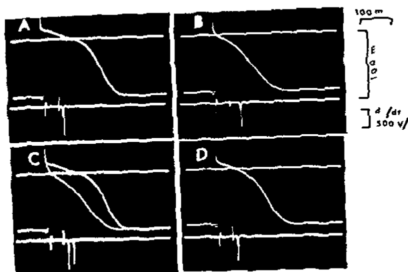


Fig 1 Effect of propranolol on the transmembrane potential recorded from a canine Purkinje fiber in a catecholamine free superfusate A shows the control action potential and differentiated record of the action potential upstroke (downward going deflection in bottom trace) B shows the action potential and differentiated up troke after superfusion with 3 0 μg/ml propranolol In C records A and B are superimposed Propranolol has markedly shortened the plateau phase and total action potential duration and has decreased upstroke velocity Maximum diastolic potential is unchanged D shows the action potential 35 minutes after return to control perfusion (Reproduced from Davis L D and Temte J V Effects of propranolol on the transmembrane potentials of ventricular muscle and Purkinje fibers of the dog Circ Res. 2? 661 1968 by permission of the American Heart Association)

act to abolish reentry in a manner analogous to quinidine or procaine amide [6] but at this time there is little evidence to support the statement

The beta receptor blocking drugs which do not have significant direct membrane effect such as sotalol and practolol still may depress action potential upstroke velocity amplitude and conduction in very high concentrations (20 μg/ml and $>$) *in vitro* [3] but such concentrations are never reached *in vivo*

Effects on action potential duration refractoriness and conduction of premature impulses In low (beta receptor blocking) concentrations beta blockers do not affect repolarization or refractoriness of atrial Purkinje or ventricular fibers when these tissues are not being superfused with catecholamines

In the presence of catecholamines the effect of beta receptor blockade is complex Beta receptor blocking drugs will reverse the accelerating effects on repolarization of isoproterenol a pure beta receptor stimulator However norepinephrine effects repolarization of atrial and Purkinje fibers by acting on both alpha and beta receptors and after beta receptor blockade the alpha adrenergic effect of norepinephrine remains For example in guinea pig atrial fibers norepinephrine lengthens action potential plateau duration by an alpha adrenergic mechanism both before and after beta receptor blockade In Purkinje fibers although norepinephrine has little effect on action potential duration in the absence of beta receptor blokade in the presence of beta receptor blockade it may increase action potential duration markedly by alpha adrenergic stimulation [3] The significance of this for the whole heart is unknown The effects of norepinephrine and beta receptor blockade on ventricular muscle fibers have not been well defined but evidence from studies on the intact heart suggests that beta adrenergic stimulation accelerates repolarization and shortens the refractory period Beta receptor blockade thus should prolong action potential duration and refractoriness in the presence of catecholamines This may be a mechanism of antiarrhythmic action particularly against reentrant ventricular arrhythmias resulting from dispersion of ventricular refractoriness due to sympathetic activation Effects of alpha receptors on ventricular muscle have not been demonstrated

Propranolol and alprenolol also alter action potential duration refractoriness and conduction of premature impulses This is due to a direct

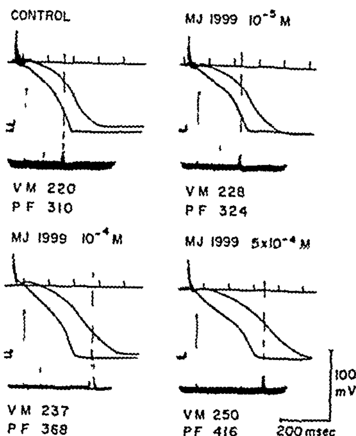


Fig 2 Effects of MJ 1999 (Sotalol) on the transmembrane potentials recorded from a canine ventricular muscle and Purkinje fiber in a catecholamine free superfusate Top trace is time markers every 100 msec *second trace* is transmembrane potential of Purkinje fiber *third trace* is transmembrane potential of ventricular muscle fiber *bottom trace* is V_m of a calibrating sawtooth pulse and the phase 0 of the Purkinje fiber action potential Under control conditions ventricular muscle and Purkinje fiber action potential durations were 220 msec and 310 msec respectively With increasing concentrations of MJ 1999 action potentials were prolonged at a concentration of 5 × 10⁻⁴ M the ventricular muscle and Purkinje fiber action potential durations were 250 msec and 416 msec respectively MJ 1999 has no effect on resting potential amplitude and peak V_{max} of phase 0 of the *Purkinje fiber action potential (Reproduced from* Strauss H C Bigger J T Jr and Hoffman B F Electrophysiological and beta receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue Circ Res 26 661 1970 by permission of the American Heart Association)

effect and occurs at concentrations higher than those needed for beta receptor blockade [11, 15, 17] Both these drugs accelerate repolarization and shorten the action potential duration of Purkinje fibers Phase 2 of repolarization is shortened more than phase 3 (Fig 1) [11, 16] Repolarization of atrial and ventricular fibers also is accelerated but by a smaller extent [11, 15, 17] The acceleration of repolarization of Purkinje fibers is most marked in areas of the ventricular conduction system where the action potential duration is greatest, this is similar to the effects of lidocaine [25] This action results in improved conduction of premature impulses in the distal conducting system, and across the gate regions [26] Since the extent to which propranolol shortens action potential duration of Purkinje fibers depends on time course of repolarization, propranolol might also abolish reentry caused by local abnormalities in action potential duration at the gates [8, 27] but this has not been demonstrated experimentally

At concentrations which have a direct membrane effect, propranolol and alprenolol both shorten the effective refractory period of Purkinje fibers but the reduction in refractory period is not as great as the reduction in action potential duration [11, 16] As a consequence the earliest premature impulses which can be initiated during repolarization arise from higher (more negative) membrane potentials They therefore have a greater V_{max} and amplitude than do the earliest premature impulses initiated prior to drug administration This effect may be antiarrhythmic in much the same manner as we have described for diphenylhydantoin [8]

Sotalol (MJ 1999) in concentrations higher than those needed for beta blockade has an entirely different effect on repolarization of Purkinje fibers and ventricular muscle cells than propranolol or alprenolol [13] The time course of repolarization is increased markedly in both fiber types as is the effective refractory period (Fig 2) Due to the high drug concentrations necessary to produce this effect it is of doubtful clinical antiarrhythmic significance Sotalol has no significant effect on repolarization of atrial muscle fibers

Practolol has a direct effect to accelerate repolarization of ventricular muscle only at the extraordinarily high concentration of 200 mg / L [1]

Effects on automaticity Beta receptor blocking drugs prevent the enhanced spontaneous diastolic depolarization caused by catecholamines These drugs will therefore slow the rate of spontaneous impulse initiation or abolish it in cells under the influences of catecholamines (Fig 3) This effect is probably one of the most important antiarrhythmic actions of beta receptor blockade The direct membrane effects of propranolol and alprenolol also may suppress spontaneous diastolic depolarization occurring in Purkinje fibers in the absence of catecholamines (Fig 4) [16, 23]

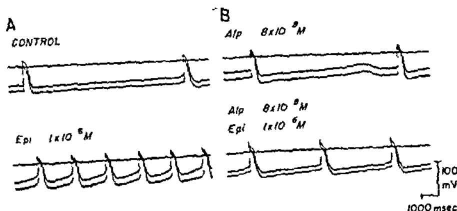


Fig 3 Effects of alprenolol on catecholamine induced automaticity in canine Purkinje fibers *The top left panel* shows the control spontaneous rate of two Purkinje fibers in the absence of epinephrine *The bottom left panel* shows the acceleration of the spontaneous rate during superfusion with 1 × 10 M epinephrine The catecholamine was then washed out of the bath and the tissue superfused with 8 × 10 M alprenolol (about 02 µg/ml) as shown in the top right panel 1 × 10 M epinephrine was again superfused in the presence of the beta receptor blocker *(bottom right panel)* note that the epinephrine enhancement of Purkinje fiber automaticity is greatly attenuated.

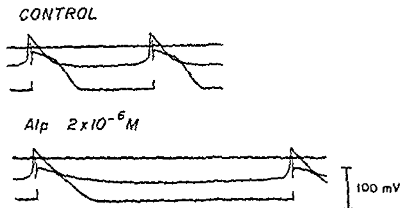


Fig 4 Direct effect of alprenolol on canine Purkinje fiber automaticity in the absence of catecholamines. *The top trace* in each panel is a time mark (10 and 100 msec) and not 0 potential *the second trace* shows the transmembrane potential recording from a *depressed Purkinje fiber* which has some spontaneous diastolic depolarization and *the bottom trace* shows the transmembrane potential recording from a more normal Purkinje fiber in the same Purkinje fiber bundle Spontaneous action *potentials are* being initiated at a cycle length of 1100 msec. in the control panel. Alprenolol 2 × 10 M (about 0 4 µg/ml.) markedly slows the spontaneous rate to a cycle length of 2400 msec as shown in the bottom panel.

Effects of beta receptor blocking drugs on the electrophysiology of the *in situ* heart

Clinically used doses of beta receptor blocking drugs probably exert most of their electrophysiological effects on the heart by blocking sympathetic influences on electrical activity therefore the electrophysiological actions of beta blocking drugs depend on the amount of autonomic activity present at the time of drug administration. If sympathetic effect on the heart is minimal beta blocking drugs will have little influence while they will cause marked changes if sympathetic activity is high Cardiac disease such as infarction or failure may result in greater sympathetic activity and therefore beta receptor blocking drugs may have a greater electrophysiological effect on the diseased than on the normal heart Cardiovascular reflexes which may be activated after administration of a beta blocking drug may also influence the response of the heart to the drug For example if blood pressure falls a decrease in vagal tone due to baroreceptor influences might offset the effects of beta receptor blockade to slow *sinus rate or A V* conduction

The electrophysiological effects also may vary between different drugs The sympathomimetic effects of practolol or alprenolol may offset some of the results of beta receptor blockade (*see below for examples*) High concentrations of drugs with direct membrane depressant actions also may influence electrical activity

Effects on the SA node *Beta receptor blocking* drugs attenuate the positive chronotropic effect which results from sympathetic stimulation When administered to experimental animals or humans in the resting state, they usually slow the sinus rate but this effect is not invariable Propranolol does not alter the heart rate in the unanesthetized dog because sympathetic tone is minimal but it will markedly slow sinus rate when administered after atropine which supposedly results in a high sympathetic tone [30] Propranolol slows the sinus rate in humans by 10 to 20 per cent [11, 36] Severe bradycardia occasionally results after commonly used doses[37] if the heart is particularly dependent on the sympathetic activity to maintain an adequate rate That the slowing usually is due primarily to beta receptor blockade and not a direct depressant effect of propranolol is indicated by comparing the actions of d l propranolol, which is used clinically, and d propranolol which has direct membrane actions but lacks beta blocking properties *d* propranolol does not significantly slow sinus rate in doses comparable to d l propranolol [39] However, the diseased sinus node may be more sensitive to the direct depressant effects of propranolol and the possibility exists that in patients with sinus node disease some slowing may result from a direct effect

Practolol,[39, 44], alprenolol [45, 46] and sotalol[47, 48] also slow the sinus rate in experimental animals, in normal human subjects and in patients with heart disease The degree of slowing which occurs probably is related to existing sympathetic tone It is uncertain whether the intrinsic sympathomimetic action of practolol or alprenolol offsets any of the sinus slowing which results from beta receptor blockade [39] None of these drugs has a direct depressant effect on the sinus node in clinically used doses[13] (Wit unpublished data)

Effects on the atria *Beta receptor blocking* drugs do not markedly affect the electrophysiologic properties of the in situ atria In both experimental animals and in humans atrial conduction is not altered and the P wave is usually unchanged [30, 36, 49, 50] However if the pacemaker site shifts as a result of the sinus slowing either within the sinus node or to an ectopic site the P wave may be altered Propranolol does not alter the effective refractory period of the atrium in unanesthetized dogs[30] but may increase it in humans [49] This increase may result from the *unopposed actions of the sympathetics on alpha* receptors in atrial muscle to prolong action potential duration Effects of other beta receptor blocking drugs on atrial refractoriness have not been studied

Effects on the AV node *Beta receptor blocking* drugs attenuate the effects of sympathetic stimulation on the AV node When propranolol is administered to experimental animals or to humans in the resting state, the P R interval may not change or it may be prolonged [30, 36] The low intrinsic sympathetic tone is probably responsible for the lack of beta receptor blocking effect on AV conduction in the unanesthetized dog If propranolol is given *after an intervention* designed to increase sympathetic tone, such as after atropine or pentobarbital anesthesia the P R interval will lengthen [30] The slowing of the sinus rate which usually accompanies propranolol administration in humans may mask its action to slow AV conduction although the P R interval prolongs in many instances [36] If heart rate is *maintained constant by atrial pacing beta receptor blocking doses of propranolol invariably* prolong the P R interval [49, 51, 52] This increase in conduction time is confined to the AV node, only the A H interval on the His bundle electrogram is lengthened [49, 51, 53] AV nodal conduction block may occasionally occur after therapeutic doses The slowing of AV nodal conduction by therapeutic doses of propranolol is usually due to beta receptor blockade and not a direct depressant *effect Doses of d propranolol, identical to* d,l propranolol doses which slow conduction are without effect on nodal conduction [51, 54] High doses of d l propranolol given to dogs do slow conduction by directly depressing the AV node[54] but these doses are not given to humans A direct depressant effect of low doses of propranolol on the diseased AV node remains a possibility and may account for some instances of conduction block

Propranolol prolongs both the functional and effective refractory periods of the AV node This indicates that AV nodal conduction of premature atrial impulses is modified [49, 54, 55] This effect on the AV nodal *refractory periods is important not*

only for slowing the ventricular response to rapid atrial rhythms but in influencing AV nodal reentry which is one mechanism for paroxysmal supraventricular tachycardia (PSVT) [5] In some patients with PSVT the atrial echo zone is shortened or AV nodal reentry of premature atrial impulses is prevented by propranolol because the slowly conducting premature impulse blocks in the node and does not return to the atrium [53] The initiation of PSVT is thereby prevented Propranolol may also produce AV nodal reentry in some patients in whom reentry is absent before drug by slowing conduction of premature atrial impulses in the node [53]

Practolol and alprenolol do not have as great an effect as propranolol on AV nodal conduction and refractoriness Practolol slows AV nodal conduction in the anesthetized dog[5] but usually does not prolong (or prolongs only slightly) the P R interval or the A H interval in humans even when heart rate is maintained constant by atrial stimulation It has been postulated that the sympathomimetic effect of practolol may counteract the slowing of conduction produced by beta receptor blockade although some investigations have failed to demonstrate a sympathomimetic effect in humans [7] Even very high doses of practolol do not have direct depressant effects on the AV node [53] The effects of practolol on AV nodal refractoriness have not been reported Alprenolol does not slow AV nodal conduction in anesthetized dogs It accelerates conduction after reserpine pretreatment as a result of its sympathomimetic effects (Wit A L Unpublished observations) In humans alprenolol slightly prolongs the A H interval in the His bundle electrogram and lengthens both the effective and functional refractory period of the AV node (Damato A N Personal communication)

Beta receptor blockade does not slow conduction through the accessory pathway in humans with WPW The effective refractory period of the anomalous pathway is also not altered [5] In patients with ventricular fusion complexes due to simultaneous activation of the ventricles via the normal A V pathway and the accessory pathway a greater degree of preexcitation occurs after propranolol due to the slowing of AV nodal conduction [5]

Effects on the ventricular specialized conducting system The beta receptor blocking drugs currently used clinically have no significant effects on conduction and refractoriness of the normal ventricular specialized conducting system Propranolol in doses up to 4 mg/kg (10 to 40 × the beta receptor blocking dose) does not prolong His Purkinje conduction time in dogs[5, 53] even when the high dose is given after conduction has previously been depressed by toxic doses of ouabain or procaine amide [5] In humans therapeutic doses of propranolol do not alter the H V interval in the His bundle electrogram and do not affect the relative and effective refractory period of the His Purkinje system [5, 2] Therefore therapeutic doses of propranolol in humans do not exert a direct depressant or quinidine like effect on the heart Practolol and alprenolol also do not alter conduction or refractoriness of the His Purkinje system in experimental animals[53] (Wit unpublished observations) or in humans[5] (Damato personal communications) even in concentrations much higher than necessary to maximally block the effects of the sympathetic nervous system

Propranolol and sotalol have both been shown to slow the idioventricular rate after complete heart block in the dog [2, 11] This is expected since pacemaker activity in the His Purkinje system presumably is under some tonic influence from both sympathetic nerves and circulating catecholamines [5, 6] Beta receptor blocking drugs also prevent the increase in idioventricular rate in response to sympathetic stimulation or catecholamine administration

Effects on ventricular muscle Beta receptor blocking drugs do not significantly affect conduction in ventricular muscle as evidenced by their lack of effect on the QRS complex of the electrocardiogram The QT interval corrected for changes in heart rate is shortened slightly by propranolol indicating some acceleration of ventricular muscle repolarization [19] Usually the effective refractory period is not changed [6] Also propranolol does not influence the ventricular excitability threshold or ventricular fibrillation threshold of the normal heart [6] However it may increase the fibrillation threshold markedly soon after coronary artery ligation in the dog Beta receptor blockade should antagonize the effects of sympathetic activation on both refractory period and fibrillation threshold

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Annotations

Virus valvular heart disease

Virus antigen has been demonstrated in the heart valves of experimentally infected animals and of patients with rheumatic heart disease [1]

Much of the evidence which supports the suggestion that viruses can cause heart disease in man has recently been reviewed It is relevant here to concentrate on experimental and clinical studies in which valvular involvement was induced or detected In 1939 Pearce described pancarditis caused by experimental virus III infection in rabbits Subsequently using a variety of other viruses he demonstrated that the incidence and severity of these changes were increased by pretreatment with one of several conditioning processes These included direct myocardial trauma and the injection of a variety of pharmacologically active reagents which he claimed operated through the common property of inducing myocardial hypoxia The implications of these findings were overlooked until the impetus of confirmed cases of viral heart disease in man in the 1950s stimulated fresh interest Several reports in the 1960s relating particularly to Group B Coxsackie virus infections described experimentally induced acute and chronic valve lesions in mice and monkeys these occurred frequently and electron microscope studies demonstrated virus particles in valve tissue Adenovirus was similarly demonstrated by other workers Macroscopically chronic valve lesions closely resembled rheumatic heart disease – for example mitral stenosis with commissural adhesions and chordal contractures Histologic changes were also similar to those of rheumatic heart disease and included lesions reminiscent of Aschoff bodies Thus in experimental animals there is convincing evidence of an association between viruses and valvular heart disease

Early reports of virus heart disease in man usually implicated Coxsackie viruses predominantly of Group B In neonates a severe and often fatal myocarditis was noted older children were less severely affected and in adults pericarditis usually dominated the clinical picture Many other viruses have since been described as causes of myocarditis and pericarditis One of these two features has characterized most reports but acute valvulitis has been diagnosed or suspected by several observers Three out of four cases recorded by Babb Stoneman and Stern had systolic murmurs in two of whom it persisted one had had a transient mitral diastolic murmur These were infants and there will remain some doubt about attributing the findings to a specific infectious illness However the similarity to cases diagnosed clinically as isolated rheumatic carditis is obvious Sainani Krompotic Slodki [1] on the other hand reporting 22 cases of adult heart disease due to Group B Coxsackie viruses noted systolic murmurs in eight cases in three of whom it was pansystolic and persistent in one case a mitral diastolic murmur also became established One of Smith s cases described as entirely healthy following an insurance medical examination had a febrile illness two weeks later and subsequently developed atrial fibrillation mitral regurgitation and a mitral diastolic murmur He had high titers to Coxsackie B virus Thus there is evidence that valve lesions may develop during the course of a viral illness and become established This evidence is obviously less impressive than in animal studies and it might be concluded from the paucity of such reports that virus induced valvular disease is at most a rarity This would however be premature for other relevant factors have to be taken into account

1 Little is known of the long term effects on the heart of mild virus illnesses although it was recently demonstrated that permanent cardiac damage can certainly result from trivial influenza perhaps in as many as 5 per cent of infected persons This could have implications for other virus illnesses which might be expected to act similarly since observed cases form only a small percentage of all infections with most viruses This is quite different from the situation which pertains to rheumatic fever in which many cases of a clinically severe illness have occurred over the years thus facilitating detailed study

2 Animal studies have clearly shown that virus valvulitis is the result of invasion from adjacent myocardium and that under appropriate circumstances this sequence of events is common There is no reason to suppose that human heart valves are any different in this respect Available evidence indicates that a virus which can cause myocarditis can also produce valvulitis

3 The concept that valve disease can develop insidiously is generally accepted Failure to detect valvular involvement during the acute stage of rheumatic fever has been no bar to attributing to it subsequent established valve disease The infrequency of documented cases of acute virus valvulitis may be to some extent a reflection of the general pattern of virus illness rather than an indication that more cases do not occur It is also likely that the numbers of reported cases will increase as interest in the subject grows

Immunofluorescent techniques adapted to detect virus antigen were employed in several of the experimental studies referred to above Although such methods have to date been used infrequently in man it has nevertheless been established that Coxsackie B virus antigen occurs frequently in the human myocardium often in the absence of clinical evidence of cardiac disease As in clinical reports the common theme of these investigative studies has been the Coxsackie B group of viruses This is understandable for available evidence indicates that this organism is the most common cause of overt viral heart disease in man However many other viruses are cardiotropic and in our present state of ignorance warrant similar attention These broader implications were the subject of a recent preliminary report [2] the first to specifically examine patients with established valvular heart disease for evidence of past viral carditis using immunofluorescent techniques Left atrial and/or valve biopsy specimens from 15 cases with acquired valvular heart disease were studied by the indirect immunofluorescent technique for evidence of antigen from a variety of viruses The salient findings were (1) virus antigen was detected in specimens from eleven out of the fifteen cases examined in the left atrial biopsy in seven cases and in valve tissue in six cases (2) Antigen from

each of the viruses studied was detected in one or more patients. The most common was echovirus in five cases (3) Antigen from more than one organism was detected in the same patient on four occasions (4) Virus antigens was detected with the same frequency in patients with and without a history of rheumatic fever Few conclusions are justified on the basis of this small series It does however establish that in patients with acquired valvular disease as in experimental animals in which valve deformities were induced, invasion of valve tissue by one or more of a variety of viruses may occur It is also clear as a corollary of this that future studies should not concentrate so exclusively on the Coxsackie group of viruses

Further work is needed to elucidate the significance of virus antigens demonstrated by this study in the valves of patients with valvular heart disease The high incidence of Coxsackie B antigen in nonvalve-disease patients suggests that synergistic interreactions of different organisms may be involved or that conditioning factors such as operate in experimental animals may also be relevant to man This will require not only an extension of the preliminary study just outlined but also an investigation of the basic problems of the pathogenicity of viruses, perhaps particularly with respect to induced autoimmune reactions such as may be involved in the production of established valvular disease Epidemiological studies are equally important to define the incidence and nature of cardiac involvement in different virus infections Unfortunately the mild often insignificant nature of many virus illnesses makes this difficult and highlights the importance of careful documentation and follow up of those few cases which are observed.

Current work which shows the concept of rheumatism as the only significant cause of acquired valvular disease is tenuous, and that many viruses may ultimately come to be implicated demands a less dogmatic approach to this subject than exists at present

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Ventricular tachycardia a new iatrogenic possibility

A prolonged Q U interval enhancing ventricular tachycardia has been reported in acute myocardial infarction hypokalemia Jervell Lange Nielsen syndrome Romano Ward syndrome and during treatment with quinidine procaineamide and phenothiazines

Recently a new iatrogenic possibility has been advanced by Picard Auzephy and Chauvin who have observed Q U prolongation ventricular tachycardia and related syncopal attacks in patients treated with prenylamine We have also observed five similar cases which confirm this new possibility

The cases have occurred in patients in which any other known cause of Q U prolongation failed and who were treated with prenylamine in normal doses (120 to 180 mg daily) Syncopal attacks produced by recurrent ventricular tachycardias disappeared in a few hours and Q U prolongation in a few days after suspension of the drug Curiously syncopal attacks and ventricular tachycardia have been described only in women of advanced age while a Q U prolongation has also been observed in men and in other age groups

Although it is useful that knowledge of this possibility is kept in mind by cardiologists it must be stressed that its

evidence is extremely rare despite large use of the drug by European patients

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Successful amputation—by whose standards?

Despite the increasing capability of the vascular surgeon to graft the smaller arteries in the leg the era of amputation for advanced vascular disease is far from finished About 80 per cent of all amputations in most western countries are made necessary by advanced ischemia Advances in surgical technique and more particularly in prosthetic technology have led to considerable optimism and to an impression that life after an amputation can be relatively unrestricted Below knee amputation an immediate postoperative prosthesis and a skillfully made patella tendon bearing or patella tendon supracondylar prosthesis would seem to promise an acceptable future for the unfortunate patient whose arteries cannot be directly reconstructed

But the vascular amputee cannot look forward to many more years of life Life tables show that about two thirds of the patients will be dead within five years[1] and those that survive face a steadily increasing risk of losing the second limb so that almost 50 per cent of five year survivors will be bilateral amputees These results may seem depressing—yet they are no worse than those achieved in the treatment of carcinoma of the breast and they are considerably better than the results of treatment of carcinoma of the stomach or pancreas

The statistics of survival are easy enough to come by and there are plenty of papers that deal with the success rate in terms of prosthetic usage Clinicians however tend to judge their results by criteria that they themselves establish Seldom is the patient given a chance to discuss his view of the outcome A recent survey of 67 vascular amputees reveals the wide disparity between the assessment of the clinician and that of the patient The amputation compelled about one patient in three to retire from active work Approximately three patients in four reported a serious decline in their social activities Although over 80 per cent were issued with prostheses and about 80 per cent of these continued to make some use of them in the long term closer analysis showed that only

about half were really independent with prostheses at an average time of three years. Despite undoubted surgical competence about a quarter of the patients reported severe and intractable symptoms related to their amputation stumps. Only about one patient in five felt that the medical staff had provided adequate support and explanation during the hospital stay. But worst of all, when the patients were asked for their assessment of the advantage of operation, only 25 per cent felt that the amputation had confered definite advantage and 15 per cent were insistent that the quality of life had deteriorated because of the amputation.

A clear picture of isolation, frustration, and resentment emerged from this survey. Granted that the patients were resentful and were probably expressing their anger by criticizing their medical care, it did appear that clinicians were poor at managing continuing problems. Their training suits them best for the management of a medical crisis, and the patients found more real support both in the short and long term from the paramedical attendants, particularly the nurses and physiotherapists.

Whether we like it or not, amputation is disabling and produces less benefit in the patient's judgment than we might like to think. Most of the amputations in this survey were carried out for intractable pain or for ulceration and limited gangrene which could not be healed by any means. Only a minority of the amputations were performed for severe and advanced toxicity which threatened life. In the western world there is a preoccupation with "integrity of the integument." Perhaps we should cease to regard an ulcer on a nonweight bearing part of the foot as an indication for amputation unless the patient is insistent that life cannot be endured because of pain and immobility. Life with a prosthesis is not regarded by elderly amputees as unfettered and enjoyable. Amputation confers gross disadvantages and ought to be reserved for those who really need it.

And if it has to be done, honest explanation, long term support, and repeated assessment must be guaranteed. It is our own finding that this support is best delivered by the paramedical staff to whom the patients relate more easily. Recall of each amputee at three-month intervals would seem to be a reasonable practice for amputation clinics, together with the mobilization of maximum help for the patient at the community level.

On the tomb of the physician Trudeau in Saranac, N. Y. are inscribed the words "To heal occasionally, to relieve often, to comfort always." We cannot cure advanced vascular disease; we can often relieve its symptoms, and there is no reason why we should not provide comfort for every patient. But these deceptively simple principles require motivation, patience, and enthusiasm, tempered by an understanding of the way our patients react to mutilation.

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Of simplifying classification of WPW syndrome (left, right, and septal types of WPW syndrome)

Various types of classification of the Wolff-Parkinson-White (WPW) syndrome have been suggested. None of these have assisted the physician by simplifying his interpretation of the electrocardiogram or by aiding in the electrophysiologic understanding of the pathophysiology of the syndrome. Since surgery has been suggested in the management of some patients with WPW syndrome, the classification of the entity into type A and type B* does not really help the practicing physician who must remember what the A and B indicate. And as would be expected, the correctness of the use of the terms is certainly indispensably important to the surgeon for proper approach to the patient. Since type A is used to indicate a pathway traversing the left side of the heart, ending in the left ventricle or left side of the ventricular septum, and type B indicates that the aberrant pathway enters the right ventricle or right side of the ventricular septum, the two types would easily be remembered and confusion eliminated if they were called "Left" and "Right WPW syndromes," respectively. The term "Septal" WPW syndrome would be used to indicate an aberrant pathway which enters the interventricular septal region of the ventricles or to indicate situations in which there is dysfunction of the atrioventricular node reflected in the electrocardiogram by short duration of the P-R segment, a QRS complex of normal duration and the absence of a delta complex. Therefore, for clinical purposes, it is suggested that the WPW syndrome be classified into left, right, and septal types. The type is readily recognized from the conventional electrocardiogram and the anatomic and functional features of the syndrome are readily understood.

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Letters to the Editor

Persistent atrial standstill in patients affected with the facio scapulo humeral (Landouzy Dejerine) type of muscular dystrophy A fortuitous risk or not?

To the Editor

In an article by Baldwin and associates entitled "Permanent paralysis of the atrium in a patient with facio scapulohumeral dystrophy" (Am J Cardiol 31 649 1973) the authors thought that there was more than a casual relation between permanent atrial standstill and this type of muscular dystrophy We are in agreement with this opinion As a matter of fact the frequency of atrial standstill is estimated by Allensworth and associates to be one case in 125 000 ECG s and, according to Morton and associates the incidence of new cases of facio-scapulo humeral dystrophy in a population is about 4 in one million births Thus one can estimate that the fortuitous risk of the association is about 1 in 30 million On the other hand, three cases of persistent atrial standstill in patients affected with the facio-scapulo humeral type of muscular dystrophy were reported on in a few years—two in the American literature If we consider that the total number of cases of Landouzy Dejerine muscular dystrophy is about one thousand in the United States according to Morton and associates, the incidence of the association of persistent atrial standstill and facio-scapulo humeral dystrophy can be estimated to be 1 in 500 which is more important than the fortuitous risk. This fact is not only theoretical. Indeed the discovery in a young patient of a persistent atrial standstill which is characterized by a regular bradycardia of junctional origin proved by His bundle recordings with a heart rate of 40 beats per minute without evidence of P waves even after pacing of the right atrium and/or the coronary sinus, implicates the systematic research of a facio scapulo-humeral muscular dystrophy A careful physical examination laboratory investigations including serum glutamic oxalacetic transaminase serum glutamic pyruvic transaminase lactic dehydrogenase creatinine and a muscle biopsy are indicated It is also necessary to examine the members of the family of the patient because the facio scapulo humeral dystrophy is a hereditary disease with a possible autosomal dominant transmission

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Etiology of atherosclerotic heart disease

To the Editor

In the lead editorial of the June issue of this JOURNAL, (AM HEART J 89 683 1975) George M Wheatley formerly chief medical director of the Metropolitan Life Insurance Company has published a great deal of information His statements that arteriosclerotic heart disease has a lesser mortality rate among middle and upper middle class people is very interesting It is a new ray of light in the epidemiology of arteriosclerotic heart disease

Furthermore Dr Wheatley refers to other articles that have come to substantially the same conclusion It may well be that those who thought stress an etiological factor in the causation of myocardial infarction may have placed the stress in the wrong economic group A picture of the stressful individual heretofore has been the hard driving assertive and aggressive executive His blue and white collar subordinates have always been thought to be more tranquil and self satisfied

Towards the end of the article however Dr Wheatley lapses back into the magical incantation of hypercholesterolemia, smoking and obesity All of us know that every good cardiologist must repeat these words three to four times daily to reaffirm his belief in what has been accepted as causative factors of this dread illness However few of these relationships have proved definitive

So far no one has found any direct effect of nicotine on the heart other than that it somewhat increases cardiac output Cardiologists today are sending poor middle aged men out on the road exercising, to achieve therefore the same results that could be obtained by a half a package of cigarettes. Over the years physicians have assumed many diseases to be caused by tobacco Had they been true the cities and towns in America today would be desolate Buffalo would once more be roaming the plains and the rivers would be again teaming with the great numbers of fish that Henry Hudson viewed in the river named for him. Furthermore the Japanese who respond as we do to tuberculosis, pneumonia and carcinoma indulge in a high rate of cigarette smoking but have a low incidence of coronary artery disease

Dr Wheatley s statistics correlate very well with experiences I have had in the practice of cardiology Many of my younger infarction patients were people who basically worked for low salaries Most of these people moonlighted on other jobs or were constantly engaged in putting additions

onto their homes They were a group who found it impossible to relax for many reasons but the need for money was one of the obvious ones Bearing this in mind perhaps it is possible to develop a unified hypothesis which might keep the cholesterol obesity and smoking factors in proper perspective

Such people since they work long hours and consume a larger amount of calories would be expected to eat more and naturally some of this food content will contain cholesterol and other fats The tension engendered by their motivation for upward mobility could easily lead to smoking Perhaps smoking serves as a stimulus to keep them awake The combined tension and high caloric intake could lead to obesity Of course this idea is only speculative

Certainly as Dr Wheatley points out there is no reason to feel that smoking or eating habits will vary so widely between socioeconomic classes The same thing should be said for exercise There is no evidence that exercise prolongs life Proponents of such programs merely state that it improves the quality of life There has also been information available showing that varsity athletes generally have a shorter survival period than we more indolent students who went to the corner soda shop after classes

Obviously Dr Wheatley s findings also constitute guilt by association But it does fit in with feelings many of us have had that stress is an important factor in the causation of premature coronary arteriosclerosis

Our primary need in cardiology today is a few heretics who will abandon the practice of equating statistical association with the etiology of atherosclerotic heart disease This would mean a greater emphasis on the causation of atherosclerosis itself We have had enough of the 25 year old chorus constantly urging the treatment of risk factors which so far have led to no accompanying reduction in mortality from coronary artery disease

The greatest importance of Dr Wheatley s paper however lies in the fact that because of his statistics we may now treat heart disease in a very pleasant manner Deprivation of food abstinence from tobacco and forced exercise may fade into oblivion and be replaced by the more enjoyable therapy of making everyone rich

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Reply

To the Editor

Naturally I am pleased that Dr Eskwith has taken the trouble to read and comment on my editorial concerning heart disease mortality statistics but I find myself at a loss to make any meaningful statement because in the absence of clinical scientific proof the only evidence we have available concerning possible etiological factors is statistical association Given these facts one must draw one s own conclusions One s personal biases no doubt influenced by one s clinical impressions will naturally lead to different conclusions from the same set of statistical facts My own conclusion from the data presented is that educational attainment reflecting no doubt higher levels of knowledge and intelligence may be the most influential factor in the multi factored etiology of arteriosclerotic heart disease Finally I would say in light of all we know and all we don t know about this disease the intelligent man (and woman) should be moderate in all things This is an old adage which appears more relevant today than ever

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Myocardial infarction in the newborn

To the Editor

I have read with great interest the paper by Drs Iannone Duritz and McCarty entitled Myocardial infarction in the newborn A case report complicated by cardiogenic shock and associated with normal coronary arteries which appeared in the February 1975 issue of the Journal (Am Heart J 89 232 1975) and would like to make two comments

First although as stated by the authors (page 234) the potential coronary vasoconstriction induced on the fetal heart by the administration of pitocin to the mother is only a remote possibility in the etiology of the diffuse myocardial necrosis in the newborn it should not be totally discarded on the basis of the absence of reported myocardial infarction in patients receiving oxytocin This is particularly true in view of the case reported by Cheng and associates on the totally unsuspected coronary vasoconstriction (spasm) leading to myocardial infarction in their patient undergoing routine coronary cinearteriography and by Brest and colleagues in their report on myocardial infarction without obstructive coronary artery disease It would indeed be very interesting to follow up the incidence of acute myocardial infarction in individuals who e mothers underwent uterine contraction augmentation with pitocin

Second the finding of diffuse myocardial necrosis and cardiogenic shock in the presence of normal coronary arteries is extremely important primarily because all of the pathophysiology studies of cardiogenic shock have been based on coronary artery ligation or occlusion It is obvious that such models are not directly pertinent to the findings reported by Dr Iannone and his co workers and it reiterates the point that there is a dire need to develop animal models which mimic left ventricular dysfunction in the presence of an uncompromised coronary circulation It should be noted here as well that the so called low output syndrome observed during or following prolonged bypass surgery tends to mimic the cardiogenic shock picture observed by Dr Iannone and may in fact lead to myocardial ischemic damage even in the presence of a normal coronary circulation To reiterate the point non occlusive animal models for myocardial failure must be developed which will complement pre-existing models based on coronary occlusion Only then will we have a more

complete picture which will encompass the findings presented in the above mentioned paper

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Reply

To the Editor

I wish to thank Dr Bonilla for his timely comments concerning our article on "Myocardial infarction in the newborn." I was particularly interested in his comments since in our researching the study we were not able to find significant evidence of pitocin causing myocardial necrosis We did not intend to totally disregard the possible relationship between the myocardial infarction and the pitocin but could find no other documentation of a correlation between the two so only mentioned it I think it is of interest as described by Brest and associates and Cheng and colleagues that there are a variety of disease processes that can cause myocardial infarction without evidence for occlusive coronary artery disease such as seen in the atherosclerotic process Although in our particular case report we found no evidence for thrombosis, hypotension probably was the etiologic factor causing massive myocardial necrosis Myocardial necrosis has been observed in the absence of obstructive coronary disease and some researchers have related this to an abnormal oxygen hemoglobin dissociation but the evidence for this has seemed to be controversial Disease of the small coronary arteries has also been alleged to be a cause of myocardial necrosis but in this particular instance we found none on the pathological specimens. There are many disease processes which we mentioned that can cause myocardial necrosis and probable infarction and the reason for this article was to illustrate another possible cause of myocardial infarction in the newborn where the disease is thought to be and probably is relatively rare

Concerning the second comments on an animal model for the observation of left ventricular dysfunction with uncompromised coronary circulation this is an area that needs further research and work Finally the possible relationship between pitocin and coronary disease in later life is conjectural at the present time but should not be discarded

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The cause of arterial disease

To the Editor

I should like to inform Drs Moshe Steier and G A Stanton (in the November 1974 issue of the JOURNAL) that as far as I know the first clinical diagnosis of coronary artery occlusion was made by Dr A Hammer Professor of Surgery in St Louis on May 4 1876 and verified by autopsy of the heart on May 6 29 hours after death

Prof Hammer was not sure if he was really the first to have made this diagnosis during the patient s life and he hesitated to publish his observations

He consulted contemporary medical authorities in New York and in some European countries during his travels All the then famous workers in medicine assured him they had never heard about a case like this Encouraged by many he did publish his observation during his stay in Vienna in 1878

In December 1899 W P Obrastzov and N D Straschesko of Kiev Russia diagnosed a case of coronary occlusion with acute myocardial infarction verified by autopsy a week later

A second case was diagnosed and at postmortem examination verified in 1908 In the same year a third case was seen

The authors published their observations in 1910 in a German medical journal.

At the end of the last and the beginning of this century medical workers were obviously not in a hurry to publish even revolutionary findings

The fact that an American and two Russian authors published their important papers in Austria or in Germany points to the dominant position these two countries held in world medicine before World War I

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Reply

To the Editor

I have noted what Dr Klobec has written as to the early reporting of cases of coronary heart attacks He has taught me one thing when discussing medical problems and that is to interpolate the words "As far as I know" For this I am grateful

At the same time I think he will agree that we can accept the finding that coronary heart disease is a problem which has arisen only during this century since at the present time there are 200 000 cases of death from this cause in England

every year and 500 000 in the U S A whereas Dr Klobec and I have managed to find after diligent search only four cases from 1876 to 1910

We must therefore accept the fact that any postulated cause of coronary attacks must be a cause which has been present only since 1875 such as chlorine in tap water and white flour and carbon monoxide in cigarettes whereas although there is a correlation with high cholesterol levels in the blood this cannot be a cause unless these levels are accompanied by the other two essential factors since such *levels have existed in man for hundreds of generations And as* to the controversy now being fought out over the respective *roles of sugar and saturated fat the mere fact that animal fat* has been eaten since primitive man first became a hunter whereas the present consumption of 150 lb of sugar per head per annum has been achieved only since 1900 proves that sugar is the arch villain and that Prof Yudkin is right to call it the Great Killer

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Reply

To the Editor

It was good to read the historical remarks of Dr Klobec Hammer s famous publication (1878) has been reproduced in English translation by Major and fully discussed by Herrick and Leibowitz However his case differs from the usual type of myocardial infarction (recent history of rheumatic fever and pathological finding of vegetations on a valve)

The important contribution to our knowledge by the paper of Obrastzow and Straschesko which *preceded* Herrick s classical paper of 1912 has been discussed by Leibowitz on pages 147-49 of his book and later supplemented in his paper (1974) Wegert Obrastzow and Herrick in the history of myocardial infarction read at the International Congress for the History of Medicine in Budapest

When I wrote my first letter to the Editor (this JOURNAL 88 677 1974) my aim was not only to quote a case of great antiquity It was to show that coronary heart disease is not a *completely new phenomenon before 1912* and to draw attention to a monograph in which its long pedigree and the *struggle to classify its clinical picture and the underlying* causes were described and documented

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Book reviews

Les Endocardites Bactériennes de l'Adulte Clinique Anatomo Pathologique Thérapeutique et Prophylaxie By Jacques Sternon Paris, 1975 Masson et Cie Editeurs, 190 pages.

Bacterial endocarditis is an ever present clinical problem The disease can offer great difficulties in clinical medium Sternon reviews the etiologic clinical manifestations and management of a series of patients with different types of bacterial infections of the valves These include for example 26 cases of staphylococcus infections of the valves 15 patients with gram negative infections, 40 patients with streptococcic infections and other patients with other types of infections of the valves The author has several general chapters concerning various problems related to subacute bacterial endocarditis such as factors related to age sex, complications, diagnosis selection of antibiotics prognosis and prevention This is a well-organized book written in French. It is a sound and practical clinical discussion of a difficult disease to diagnose and treat at times

Intensive Coronary Care By Michael F Oliver Desmond G Julian and Myra G Brown Geneva 1974 World Health Organization 80 pages.

This small manual is designed for training the nursing staff of coronary and intensive care units. The discussions are clear and the illustrations simple The authors present briefly the anatomy of the coronary arteries their function and pathology as well as the common clinical manifestations of coronary heart disease Cardiac arrythmias are discussed Treatment of patients with various illnesses is emphasized The rationale of medication and other therapeutic measures are lucidly presented. This is a valuable simple manual which should interest the nursing staffs of coronary and intensive care units

Non-Invasive Methods in Cardiology Edited by Samuel Zoneraich, M D Springfield, Ill. 1974 Charles C Thomas Publisher 583 pages.

This book, edited by Zoneraich, contains a practical review of the "non invasive technical procedures now employed in cardiology It is unfortunate we have diagnostic procedures that "invade the health of man Even drugs do this chemically or pharmacologically Because of their hazards and costs the invasive" diagnostic procedures should be used only when necessary which is seldom As would be expected from its title this book contains a fundamental practical discussion of recordings of heart sounds, venous and arterial pulses, apex beat and electrical activity of the heart The applications of these technical procedures are discussed The illustrations are very good and the text is clearly written This is a good book on the subject for all physicians and especially for cardiologists who need to use invasive diagnostic measures much less frequently

A System of Vectorcardiographic Interpretation By A. Calhoun Witham, M D Chicago 19 5 Year Book Medical Publishers, Inc., 472 pages.

Vectorcardiography (VCG) is being used in clinical practice with increasing frequency The reason for this is not clear Its value in clinical practice has not been shown to be very great if it is of much use at all. Nevertheless, Witham s book is now timely He reviews the principles of VCG and has used the Helm system of reference for recording the many representative tracings contained in the atlas The book is intended for clinicians and is written in that vein The atlas contains clinical and electrocardiographic information with each figure and, of course, the VCG interpretations. Witham wisely included a set of ECG leads along with the VCG The experienced electrocardiographer could obtain all the information he needed from the ECG without the VCG However this reviewer has always made it a practi e to interpret the VCG with the accompanying ECG All illustrations are good and the principles discussed in the text are sound In general the VCG concepts are well presented. Of course it is easy to find isolated aspects of any book which might be improved or which are not clear This reviewer might indicate one e g the figure on page 4 shows a sketch of a man who is supposed to illustrate the frontal view However a glance at this illustration suggests the view is not frontal but a posterior view Regardless of such minor problems this publication is a useful one for those who wish to review VCG The physician should know ECG well first and if he does VCG can add a little more to his diagnostic armamentarium

Echocardiography Case Studies By Jack J Kleid, M D., and Nelson B Schiller M D Flushing N Y., 1974 Medical Examination Publishing Company Inc.

As the title of this booklet indicates this publication includes a series of case histories (58 in number) in which echocardiograms (ECHO) were employed in the clinical evaluation of the patients The photographs of the ECHO are in general good even though some of the recordings are not uniformly very good. This is due mainly to the present imperfections of the procedure Nevertheless echocardiography is so important and valuable in cardiology that readers will find this booklet of case studies to be valuable practical and a good training experience This book is worth owning It should interest all cardiologists and physicians interested in learning echocardiography

Exercise and Coronary Heart Disease Role in Prevention Diagnosis Treatment By Gerald F Fletcher M D and John D Cantwell, M.D Springfield Ill. 1974 Charles C Thomas Publisher 2o4 pages

Fletcher and Cantwell have produced a book which should not only interest internists, cardiologists and other physicians but patients as well. They discuss the various forms of exercise used in therapy and in maintaining good health. The exercise testing technics used in clinical practice such as the Master s two-step and various treadmill exercises are clearly described The book contains illustrations of various exercise procedures used to maintain cardiac health. The illustrations are supported by a text describing the instructions reasons and precautions related to exercise in rehabilitation in cardiology The authors are convinced that the formal exercise programs are good for cardiac patients. This may be true but the book is not convincing in this regard. The book is written to present exercise as a therapeutic agent for the management of heart disease not only in prevention of coronary heart disease but also to prolong life It is a detailed presentation an aspect of the book physicians should welcome Physicians and patients who are interested in the use of exercise in cardiology will find this to be a profitable single source on the subject

Atherosclerosis III Edited by G Schettler and A Weizel New York 1974 Springer Verlag 1034 pages Price $32 00

These are the proceedings of the Third International Symposium on arteriosclerosis The number of participants in the symposium and the number of authors who contributed to this volume are considerable The contributors are from many parts of the world Unfortunately this reviewer found nothing *new or exciting about this extremely important* disease of man For the most part the same contributors presented much the same data that they have presented at other symposia The greatest reason for such symposia is to keep interest alive There is a need however to have smaller symposia and smaller size publications but with new thoughts and approaches to the pathogenesis of arteriosclerosis The reader will find this publication to represent a good review of the present state of knowledge concerning the etiology prevention diagnosis and management of arteriosclerosis After many years of effort very little change has taken place in the incidence of arteriosclerosis and its complications Surely this is to be expected Arteriosclerosis is a most difficult disease to control and to learn its pathogenesis is also difficult All physicians will find a great deal of interesting information in this book

Quantitive Nuclear Cardiography Edited by Richard N Pierson Jr M D Joseph P Kriss M D Robert H Jones M D and William J MacIntyre Ph D New York 1975 John Wiley & Sons Inc Publishers 289 pages Price $24 50

This book edited by Pierson and colleagues is misleading to this reviewer The title would suggest that nuclear medical methods as applied to cardiology are sufficiently quantitative so that the problems in cardiology which need more accurate and sensitive quantitative procedures and measurements are answered by nuclear cardiology One who has worked with the problem knows how crude the nuclear methods are and he also knows of the *more sensitive technics* needed in clinical cardiology That nuclear methods have a place in cardiology is not the question This is accepted by all cardiologists But accurate sensitive quantitation is a different matter For example measurement of regional perfusion of the myocardium by nuclear medical methods is crude and very inaccurate in laboratories of clinical nuclear medicine and even in the most sophisticated research laboratories Nevertheless this book with its many contributors has summarized the problems very well The methods employed are nicely presented and the need to improve clinical and experimental nuclear cardiology are evident from this book The illustrations of recordings also reveal very well the state of knowledge for the present time Cardiologists should know what nuclear medicine has to offer to clinical practice This book is recommended to all cardiologists as an important single source of important information

Thromboembolism Etiology Advances in Prevention and Management Edited by A N Nicolaides Baltimore 1975 University Park Press 318 pages Price $29 50

This book edited by Nicolaides is important and valuable Its contributions have produced in a single volume a review *for the reader of the important problems related to throm*boembolism Thromboembolism is a common and hazardous disease This is a well written and organized book produced for the clinician The major aspects of thromboembolism are considered in a concise and practical manner A critical reader readily notes the deficiencies in knowledge about thromboembolism The figures are simple the bibliography is good and *the information imparted is well selected As with all books* these days, the price is high

***The* Assessment and Performance of Implanted Cardiac Pacemakers** By E E Green London 1975 Butterworth & Co Ltd 214 pages

The use *of pacemakers and the dependence upon* their function for the lives of people is already great and is constantly increasing Because of this there is a need to periodically assess the state and future reliability of an implanted pacemaker Green a biophysicist with this book has rendered a service to all cardiologists and pacemaker clinics and to people who depend upon constant functioning of their pacemakers *It is a small book* which concisely describes the pacemaker assessment and performance Being an experienced physicist Green lucidly indicates how to evaluate the function of a pacemaker This is done very well This is a very good publication which should be read and studied by all physicians who are involved in the use of cardiac pacemakers in medicine

Books received

Medical Aspects of Drug Abuse Edited by Ralph W Richter MD FACP Hagerstown Md 1975 Harper & Row Inc 373 pp

The Heart Watchers Cookbook By Celia [illegible]orman New York 19 5 Hippocrene Books Inc 224 pp Price $8.95

Coping with Prolonged Health Impairment in your Child By Audrey T McCollum MS, Boston 1975 Little Brown & Company 340 pp Price $10 00

The Science of Life Edited by K D Fisher and A U Nixon New York 1975 Plenum Publishing Corp 348 pp

Glycosaminoglycans and Arterial Disease By Roger W Robinson Ivan N Likar and Lydia J Likar Basel Switzerland, 1975 S Karger AG 134 pp Price $31.50

Actualités Cardio-Vasculaires Médico-Chirurgicales By R Froment A Gonin P Michaud A Perrin and J Descotes Paris 1975 Masson & Cie Editeurs 224 pp

The Mammalian Myocardium Edited by Glenn A Langer and Allan J Brady Somerset N.J., 1975 John Wiley & Sons Inc 305 pp

Principles and Techniques of Human Research and Therapeutics vol VI Drugs Useful vs Infectious Diseases Edited by F Gilbert McMahon MD Mount Kisco N Y 1975 Futura Publishing Co 144 pp Price $14 95

Principles and Techniques of Human Research and Therapeutics vol VII *Endocrine Metabolic Drugs* Edited by F Gilbert McMahon MD Mount Kisco N Y 1975 Futura Publishing Co 222 pp Price $11 00

Principles and Techniques of Human Research and Therapeutics vol VIII *Psychopharmacological Agents* Edited by F Gilbert McMahon MD Mount Kisco N Y 1975 Futura Publishing Co 290 pp Price $17 00

Principles and Techniques of Human Research and Therapeutics vol IX *Evaluation of Gastrointestinal Pulmonary Anti Inflammatory and Immunological Agents* Edited by F Gilbert McMahon MD Mount Kisco N Y., 1975 Futura Publishing Co., 243 pp Price $14 95

Announcements

World Congress on vascular diseases

A World Congress on Progress in Vascular Diseases will be held in Bombay India on March 19 through 21 1976 The congress will be under the auspices of the Western Indian chapter of the American College of Chest Physicians A variety of subjects pertaining to cardiovascular and pulmonary vascular disorders will be presented For further information please write Dr M Paul Anand Secretary General 4 Narendra Bhuvan Warden Road Bombay 400 026 India

Seventh annual conference of the Retina Service of the Wills Eye Hospital

The Retina Service of the Wills Eye Hospital and Jefferson Medical College of Thomas Jefferson University will co sponsor a comprehensive course on Vascular Diseases of the Ocular Fundus on March 6 and 7 1976 This course will cover anatomy physiology pharmacology fluoroangiography as well as disorders of the vessels disorders of the blood constituents maculopathies vascular tumors anomalous vascular formations medical and surgical concepts and oculo-cerebral problems The tuition will be $175 00 with a special rate of $60 00 for residents and fellows For further information hotel reservations and wives Bicentennial activities write to Richard F Goldberg M D Retina Service Wills Eye Hospital 1601 Spring Garden St Philadelphia Pa 19130 This is a Continuing Medical Education offering

Seminar on urology

The Seventh International Course of Urology organized by the Department of Urology of the University of Barcelona will be held in the second week of April 1976 in the School of *Medicine and University Clinic Hospital Barcelona Spain* The course will last five days Operating sessions will be held in the mornings and lectures and films will be presented in the afternoons The sessions will be led by Professors J M Gil Vernet and W Gregoir Recognized authorities from Spain France Belgium Austria Czechoslovakia Germany Britain and the United States will participate There will be simultaneous translations into English French German and Spanish

For further information please write Secretary Department of Urology School of Medicine University of Barcelona Casanovas 143 Barcelona 11 Spain Telephone 34 3 254 45 56

Congress of Pan Pacific Surgical Association

The Fourteenth Congress of the Pan Pacific Surgical Association will be held from April 1 through 7 1978 at the Hilton Hawaiian Village Hotel Honolulu Hawaii Concurrent meetings will be presented on General Surgery Neurosurgery Obstetrics and Gynecology Ophthalmology Orthopedic Surgery Otolaryngology Plastic Surgery Thoracic Cardiovascular area and Urology

For further details write Cesar B deJesus M D Pan Pacific Surgical Association 236 Alexander Young Bldg *Honolulu Hawaii 96813*

Refresher course in cardiac radiology

A refresher course in cardiac radiology will be presented by the North American Society for Cardiac Radiology March 21 to 25 1976 at the Sir Francis Drake Hotel San Francisco California The program will include didactic and seminar presentations of topics dealing with the radiology of pediatric and adult heart disease as well as discussions of new techniques in cardiac diagnosis and a scientific session for all participants For further information please write to Erik Carlsson M D Department of Radiology University of California San Francisco CA 94143

Bioengineering conference

The fourth annual New England Bioengineering Conference will be held at Yale University New Haven Conn on *May 7 and 8 1976* The deadline for abstracts of papers to be presented is December 15 1975

Forward all abstracts and requests for further information to Prof Subrata Saha Dept of Engineering and Applied Science Yale University Becton Center 15 Prospect St New Haven Conn 06520 Telephone (203) 432-4474 You may also contact James A Albright M D Section of Orthopaedic Surgery Department of Surgery Yale University School of Medicine 333 Cedar St New Haven Conn 06510 Telephone (203) 436 3231

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The Retina Service of the Wills Eye Hospital and Jefferson Medical College of Thomas Jefferson University will co sponsor a comprehensive course on Vascular Diseases of the Ocular Fundus on March 6 and 7 1976 This course will cover anatomy physiology pharmacology fluoroangiography as well as disorders of the vessels disorders of the blood constituents maculopathies vascular tumors anomalous vascular formations medical and surgical concepts and oculo-cerebral problems The tuition will be $175 00 with a special rate of $60 00 for residents and fellows For further information hotel reservations and wives Bicentennial activities write to *Richard E Goldberg M D Retina Service Wills Eye Hospi*tal 1601 Spring Garden St Philadelphia Pa 19130 This is a Continuing Medical Education offering

Seminar on urology

The Seventh International Course of Urology organized by the Department of Urology of the University of Barcelona will be held in the second week of April 1976 in the School of Medicine and University Clinic Hospital Barcelona Spain The course will last five days Operating sessions will be held in the mornings and lectures and films will be presented in the afternoons The sessions will be led by Professors J M Gil Vernet and W Gregoir Recognized authorities from Spain France Belgium Austria Czechoslovakia Germany Britain *and the United States will participate There* will be simultaneous translations into English French German and Spanish

For further information please write Secretary Department of Urology School of Medicine University of Barcelona Casanovas 143 Barcelona 11 Spain Telephone 34 3 254 45 56

Congress of Pan Pacific Surgical Association

*The Fourteenth Congress of the Pan Pacific Surgical Asso*ciation will be held from April 1 through 7 1978 at the Hilton Hawaiian Village Hotel Honolulu Hawaii Concurrent meetings will be presented on General Surgery Neurosurgery Obstetrics and Gynecology Ophthalmology Orthopedic Surgery Otolaryngology Plastic Surgery Thoracic Cardiovascular area and Urology

For further details write Cesar B deJesus M D Pan Pacific Surgical Association 236 Alexander Young Bldg Honolulu Hawaii 96813

Refresher course in cardiac radiology

A refresher course in cardiac radiology will be presented by the North American Society for Cardiac Radiology March 21 *to 25 1976 at the Sir Francis Drake Hotel San Francisco* California The program will include didactic and seminar presentations of topics dealing with the radiology of pediatric and adult heart disease as well as discussions of new tech*niques in cardiac diagnosis and a scientific session for all* participants For further information please write to Erik Carlsson M D Department of Radiology University of California San Francisco CA 94143

Bioengineering conference

The fourth annual New England Bioengineering Conference will be held at Yale University New Haven Conn on May 7 and 8 1976 The deadline for abstracts of papers to be presented is December 15 1975

Forward all abstracts and requests for further information to Prof Subrata Saha Dept of Engineering and Applied Science Yale University Becton Center 15 Prospect St New Haven Conn 06520 Telephone (203) 432-4474 You may also contact James A Albright M D., Section of Orthopaedic Surgery Department of Surgery Yale University School of Medicine 333 Cedar St New Haven Conn 06510 Telephone (203) 436 3231

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